Supreme Court, U.S.
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In The

Supreme Court of the United States

NUTRACEUTICAL CORPORATION; SOLARAY, INC.,

Petitioners,

v.

ANDREW VON ESCHENBACH, COMMISSIONER, U.S. FOOD AND DRUG ADMINISTRATION; U.S. FOOD AND DRUG ADMINISTRATION; MICHAEL O. LEAVITT, SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES; DEPARTMENT OF HEALTH AND HUMAN SERVICES; AND THE UNITED STATES OF AMERICA,

Respondents.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Tenth Circuit

PETITION FOR A WRIT OF CERTIORARI

RICHARD A. EPSTEIN
111 East 60th Street
Chicago, IL 60637
(773) 702-9563

JONATHAN W. EMORD
Counsel of Record
EMORD & ASSOCIATES, P.C.
1800 Alexander Bell Drive
Suite 200
Reston, VA 20191
(202) 466-6937

Counsel for Petitioners

COCKLE LAW BRIEF PRINTING CO. (800) 225-6964
OR CALL COLLECT (402) 342-2831

QUESTIONS PRESENTED

(1) May the FDA subject dietary supplements, which are unambiguously classified as foods under the Food, Drug and Cosmetic Act, to the safety and effectiveness review that the FDCA explicitly reserves for drugs, without a specific statutory warrant to that effect?

(2) May the FDA discharge its statutory burden of proof for showing that Petitioners' dietary supplements (containing 10 mg or less of ephedrine alkaloids per daily dose) present a risk of illness or injury *at the dose levels recommended or suggested in labeling* solely by offering evidence that chemically distinct products (drugs), absorbed in different ways (intravenously), may cause harm at unspecified dose levels?

(3) Does the statutory phrase "presents a significant or unreasonable risk of illness or injury" under "conditions of use recommended or suggested in labeling" allow the FDA to ban ephedrine alkaloid containing dietary supplements (EDS) at every dose level, when it lacks proof of risk at the recommended daily dose levels of 10 mg or less, solely because FDA deems the health benefits of the dietary supplement insubstantial?

(4) Did the Tenth Circuit violate its statutory duty to decide "any issue under [21 U.S.C. § 342(f)(1)] on a de novo basis" when it held all findings in FDA adulteration rulemakings not reviewable de novo?

PARTIES TO THE PROCEEDING

All of the parties are listed in the caption of the petition.

CORPORATE DISCLOSURE STATEMENT

Solaray, Inc., a Utah corporation, is wholly owned by Nutraceutical Corporation, a publicly-held corporation. Nutraceutical, a Delaware corporation, is wholly owned by Nutraceutical International Corporation, a publicly-held corporation.

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FDA, *Guidance for Industry: Premarket Risk Assessment*, 5, n.4 (2005) 8

OPINIONS BELOW

The opinion of the court of appeals (App. 1-21) was entered on August 17, 2006 and is reported at *Nutraceutical Corp. v. Von Eschenbach,* 459 F.3d 1033 (10th Cir. 2006). The order of the court of appeals denying rehearing (App. 44-45) was entered on October 16, 2006 and is unreported. The opinion of the district court (App. 22-43) was entered on April 14, 2005 and is reported at *Nutraceutical Corp. v. Crawford,* 364 F. Supp.2d 1310 (D. Utah 2005). The final rule of the Food and Drug Administration (excerpts in App. 46-128) is reported at Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, 69 Fed. Reg. 6788 (Feb. 11, 2004) ("Final Rule").

JURISDICTION

The court of appeals' judgment was entered on August 17, 2006. A timely petition for rehearing was denied on October 16, 2006. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

STATUTORY PROVISIONS INVOLVED

Section 402(f)(1) of the Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. § 342(f)(1) (2006), as enacted by § 4 of the Dietary Supplement Health and Education Act of 1994 ("DSHEA"), Pub. L. No. 103-417, 108 Stat. 4325 (1994), provides:

A food shall be deemed to be adulterated –

* * *

(f)

(1) If it is a dietary supplement or contains a dietary ingredient that –

(A) presents a significant or unreasonable risk of illness or injury under –

(i) conditions of use recommended or suggested in labeling,

or

(ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use;

* * *

In any proceeding under this subparagraph, the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated. The court shall decide any issue under this paragraph on a de novo basis.

21 U.S.C. § 321(ff), section 201(ff) of the FDCA, defines "dietary supplement:"

(ff) The term "dietary supplement" –

(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

(A) a vitamin;

(B) a mineral;

(C) an herb or other botanical;

(D) an amino acid;

> (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
>
> (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E);
>
> * * *
>
> Except for purposes of section 201(g) [subsec. (g) of this section], a dietary supplement shall be deemed to be a food within the meaning of this Act [21 USCS §§ 301 et seq.].

The other relevant statutory provisions are reproduced in the appendix. App. 129-137.

STATEMENT

1. The Statutory Background of the FDA Final Rule on Ephedrine Alkaloids

This case raises the important and recurring question of what standards the FDA must follow in banning dietary supplements from the market. Under the FDCA, dietary supplements are classified as foods. 21 U.S.C. § 321(ff). As such, the FDA may remove them from the market only if they are found to be adulterated. 21 U.S.C. § 342. The suppliers of foods are not required to prove a health benefit when faced with a claim of adulteration. 21 U.S.C. § 342(a)-(e). Nor does the FDCA require manufacturers of foodstuffs to present them to the FDA for approval prior to their being marketed. Instead, the statute explicitly places on FDA the burden to prove foods adulterated before it may order their removal from the market. By contrast, the FDCA prohibits the entry of drugs into the market unless

they have been proven to produce a benefit that counterweighs risk of harm. 21 U.S.C. § 355(b)(1)(A).

Prior to 1994, dietary ingredients were regulated under the food subparts of the FDCA Adulterated Food section. See 21 U.S.C. § 342(a),(b),(c) (1994). Under 21 U.S.C. § 342(a)(1), if a substance is not one added to a food, it may not be deemed adulterated unless "the quantity of such substance in such food" ordinarily renders it "injurious to health." 21 U.S.C. § 342(a)(1). In instances where an ingredient naturally occurs within a food, the FDA has to prove by a preponderance of the evidence that the actual quantity of the ingredient in the food ordinarily renders the food "injurious to health," i.e., FDA must prove a dose-response relationship. See e.g., *United States v. 5 cases more or less containing 'Figlia Mia Brand,'* 179 F.2d 519, 524 (2d Cir. 1950). The dose-response relationship is a central underpinning of adulteration law and science, the very principle "on which the science of toxicology is based." *"Dose-Response Relationships in Toxicology,"* Extension Toxicology Network (1993) (pmep.cce.cornell.edu/profiles/extonet/TIB/dose-response.html); see also *United States v. Lexington Mill Co.*, 232 U.S. 399, 412 (1914). The concept has been the grand and irreducible tenet of toxicology since at least the 16th Century. In the early 1600's, Swiss Physician Philippus Theophrastus Aureolus Bombastus von Hohenheim Paracelsus (Paracelsus) wrote, "[a]ll things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison." J. L. Goodman, *"The Traditional Toxicologic Paradigm Is Correct: Dose Influences Mechanism,"* 106 Environ. Health Perspectives 285, 288 (1988). The dose-response relationship, the so-called Paracelsian axiom, is embedded in adulteration law.

In 1994, Congress amended the Adulterated Food section of the FDCA to include a subpart dedicated to dietary supplements. Dietary Supplement Health and Education Act ("DSHEA"), 21 U.S.C. § 342(f), Pub. L. No. 103-417, 108 Stat. 4325 (1994). Congress drafted its Section 342(f)(1)(A)(i) amendment to reiterate and reconfirm the principle that dose determines toxicity. In the legislative history, Congress writes, "FDA . . . [is] required to describe how risks are presented under 'the conditions of use recommended or suggested in labeling' and FDA [is] thus required to consider whether certain conditions of use would not present a substantial and unreasonable risk of illness or injury," S. Rep. No. 103-410 at 35 (1994). Under Section 342(f)(1)(A)(i), a dietary supplement is adulterated if it "(A) presents a significant or unreasonable risk of illness or injury under – (i) conditions of use recommended or suggested in labeling." To meet its burden of proof under that section, FDA must establish risk of illness or injury at the dose level recommended or suggested in labeling. In Petitioners' case, that dose level is 10 mg or less EDS per daily dose. As explained below, FDA never met its burden of proof, never demonstrated that EDS at 10 mg or less per day presents a risk of illness or injury, yet banned all EDS from the market at every dose level when contained in a dietary supplement. Ironically, in its Final Rule FDA expressly exempts from the ban all EDS in conventional foods and in over-the-counter (OTC) Asian medicines, regardless of dose. App. 72.

2. The FDA Proceedings

Before FDA imposed its ban on EDS, petitioners sold a dietary supplement consisting of whole crushed ephedra sinica herb placed in gelatin capsules standardized to contain 10 mgs or less of ephedrine alkaloids per daily

dose. Millions of doses were consumed safely, without illness or injury. On April 7, 2003, the petitioners submitted comments to the FDA to demonstrate that there was no credible scientific evidence of any serious adverse event resulting from daily ingestion of EDS at 10 mgs or less. Exhibit C to Plaintiffs' Mot. for Summary Judgment. They urged FDA to exclude from any rule restricting the sale of EDS dose amounts equal to or less than 10 mgs per day. *Id.* The herbal content in petitioners' dietary supplement is precisely the same substance used in ephedra tea, a food FDA exempts from the Final Rule ban. App. 72. The record evidence revealed ephedra tea to yield between 15 to 30 mg or more of ephedrine alkaloids per serving, with users often consuming multiple tea servings at meal time. FDA Briefing Materials for Food Products Containing Ephedrine Alkaloids, Docket 95N-0304, Vol. 39, Ref. 1, at 5 (Oct. 11-12, 1995). Unlike other companies' ephedra products, the petitioners' contained no added or synthetic ephedrine, a drug, and no claims of any physiological effect. Exhibit B to Plaintiffs' Mot. for Summary Judgment.

Although FDA refused to permit any exception to its ban on dietary supplements, it did exclude from its ban all ephedrine alkaloid containing foods as well as all traditional OTC Asian medicines (regardless of ephedrine alkaloid dose). Therefore, it limited its ban to dietary supplements. See App. 70-73. The FDA decision thus produced the illogical and irrational result of removing ephedrine alkaloids at every quantitative amount from the market when in dietary supplements but of not removing ephedrine alkaloids in any quantitative amount from the market when in other foods. The Final Rule thus prohibited petitioners from selling their raw crushed ephedra sinica herb in a gelatin capsule (a dietary supplement

form) but did not prohibit them from selling the very same substance as a tea (a food form). The FDA decision thus defines adulteration law in a way that discriminates based on the *form* of dietary ingredient rather than on the *substance* of the ingredient, such that dietary ingredients sold as foods or as traditional OTC Asian medicines enjoy a statutorily protected position denied dietary ingredients sold as dietary supplements.

To reach this odd result, the FDA had to adopt a novel standard for proving ephedrine alkaloids harmful, a standard applicable to all dietary supplements and in conflict with the pre-existing standard for foods, including dietary supplements. The standard, adopted for all dietary supplements, not just EDS, fundamentally alters adulteration law for those products. Its Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, 69 Fed. Reg. 6788 (excerpts App. 46-128), was published on February 11, 2004. In it, FDA declared dietary supplements adulterated if they contained so much as a *single* molecule of ephedrine alkaloids. The FDA did not rely on any direct evidence to establish the dose level at which toxicity occurred (it thus abandoned the Paracelsian axiom at the heart of adulteration law); nor did it perform or commission any tests on the effects of ephedrine alkaloids when used at the 10 mg or less level; nor did it perform any test on ephedrine alkaloids at all. Instead the FDA adopted a new adulteration test, see App. 75 ("[FDA is] articulating a standard for unreasonable risk under 402(f)(1)(A) of the [FDCA] for the first time . . . "). In so doing it took the interpretive leap of equating the "unreasonable risk" statutorily prescribed for dietary supplements with the "safe and effective" standard that the FDCA uses to assess whether new drugs may be granted

approval to enter the market. See FDA, 21 U.S.C. § 355(b)(1)(A); see also *Guidance for Industry: Premarket Risk Assessment*, 5, n.4 (2005) (associating FDA's "risks and benefits" test with statutory requirements that drugs be safe and effective). Thereafter, without specific statutory authorization, FDA adopted the following three-step approach.

> Step 1. The FDA read the statutory words "unreasonable risk" to permit the FDA to use a generalized risk/benefit standard to determine whether a dietary supplement should remain on the market. App. 75, 105-116.
>
> Step 2. The FDA assigned minimal health benefits to ordinary uses, including important consumer objectives such as weight loss, enhanced athletic performance, increased energy levels, easier breathing, and other uses, finding among them only weight loss sufficient to warrant critical assessment. FDA then determined that scientific evidence concerning those effects assessed "short term" rather than "long term" weight loss, and "short term" weight loss was not a significant health benefit according to FDA. App. 119-121.
>
> Step 3. The FDA hired Dr. Mario Inchiosa to evaluate the scientific literature on the effects of intravenously injected drugs epinephrine and ephedrine, effects it claimed would occur in orally ingested EDS. Inchiosa's untested assessment, in the form of letters of opinion, concluded that no clear evidence established that the drugs epinephrine and ephedrine were safe at any dosages. Dr. Inchiosa created his own unique unpeer-reviewed and untested hypothetical extrapolation in which he presumed EDS would affect the body in a manner chemically

> indistinguishable from ephedrine and epinephrine, both potent drugs. He extrapolated from the studies involving intravenous injection of those drugs, even though the dietary ingredient is orally ingested. He assumed comparable effects, despite the fact that the drugs are very potent inducers of rapid heart contractions and elevated blood pressure and directly affect parts of the body that the dietary ingredient does not. He employed a mathematical model never before used in pharmacology or toxicology to compare the drugs with the dietary ingredient. Based on those unconventional and unprecedented techniques, he concluded that continuous ingestion of 1.5 mg of ephedrine alkaloids every four hours would present a risk of injury comparable to the drugs. Neither Dr. Inchiosa nor anyone else at FDA ever discussed, let alone evaluated clinically, ingestion of 5 mg or less of ephedrine alkaloids twice daily at meal times, the actual dosing in the conditions of use for the petitioners' product. Dr. Inchiosa's letters were not peer-reviewed. His hypothesis was never tested. His conclusions of toxicity were not based on any clinical testing of the actual dietary ingredient at any dose level, let alone 10 or fewer mg. The drug-dietary ingredient comparison model he invented was not adopted through scientific consensus and is not a standard method for pharmacological or toxicological evaluation, yet that comparison acquired decisional significance in the Final Rule's assessment of low dose ephedra. App. 101.

On the strength of this record, the FDA concluded that it had carried its burden of proof that ephedrine alkaloids posed a risk of illness or injury at every dose level, including daily dose amounts of 10 mg or less, justifying a total ban. In words that track the statute:

> The [FDA] is issuing a final regulation declaring dietary supplements containing ephedrine alkaloids adulterated under the [FDCA] because they present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in labeling, under ordinary conditions of use.

App. 46.

As should be apparent from the FDA's calculated omission of the word "significant" in the quoted passage, the FDA did *not* find that ephedrine alkaloids posed a "significant risk" of harm. Its ruling is therefore wholly consistent with the proposition that ephedrine alkaloids may present at 10 mg or less per daily dose amounts only a miniscule risk of harm in their specified use. Stressing the word "or" as disjunctive in the phrase "significant or unreasonable risk" (and ignoring "significant risk" entirely), the FDA concluded solely that the risk, however small, was unreasonable in light of the minimal health benefits it stated the substance provided. FDA therefore concluded that it was wholly "unnecessary" to ask whether the risk was significant because the term was included in the statute as a strict alternative to the phrase "unreasonable risk." App. 70 ("We are not addressing the issue of whether these products present a 'significant' risk under section 402(f)(1)(A) of the act"); see also Def. Mem. Supp. Cross-Mot. Summ. J. at 31 n.14 ("Because the FDA concluded that EDS pose an unreasonable risk, it was not necessary for the agency to address DSHEA's significant risk standard"). In sum, the FDA's position is that ephedrine alkaloids present an insignificant, but unreasonable risk of illness or injury at 10 mg or less (but no significant health benefit at any dose).

3. The District Court Proceedings

The petitioner then challenged the use of these procedures in District Court, which held the Adulterated Food section of the FDCA, 21 U.S.C. § 342(f)(1), unambiguous under Step 1 of *Chevron USA, Inc. v. Nat. Res. Def. Council, Inc.*, 467 U.S. 837 (1984). The District Court held that section 341(f) unambiguously required FDA to perform an examination of all dietary ingredients to determine whether their toxicity met the statutory test for adulteration at recommended or suggested dosages. App. 40-42. The District Court therefore refused to credit general evidence that showed some correlation between the intake of EDS at unspecified levels above 10 mgs per daily dose with heart attacks and other adverse events because these reports were not tied to the dose-specific measures set out in the statute. See App. 40-42. Likewise, it dismissed the 3,000 or so adverse event reports (AERs) submitted annually, because none of these were dose related or causally proven. Finally, it refused to credit Dr. Inchiosa's opinion letters because they shared the common defect of never examining the bodily intake of EDS at specified dose levels. App. 40-42. The District Court noted that he only examined the drugs epinephrine and ephedrine, which are distinct substances absorbed at different rates and through different mechanisms, in order to infer the rates of bodily absorption of EDS. Epinephrine is known to be far more potent than EDS. Yet the District Court noted that Dr. Inchiosa failed to validate the mathematical model he used to justify the conversion rate from epinephrine to EDS, by hedging his final conclusion: "In the absence of a clinical indication, it would not be possible to recommend a safe dose of ephedra." Inchiosa letter, discussed at App. 41-42. Therefore the District Court

concluded that Dr. Inchiosa did not establish that EDS presented a significant or unreasonable risk of illness or injury at the 10 mg or less daily dose amount. App. 42. The District Court also found that all the testimony presented at the FDA's food advisory committee meeting took this same inverted form. None of the physicians present offered evidence of EDS danger at a specified level of ingestion. Rather, "[s]everal of the meeting's attendees made comments that a safe level could not be determined." App. 42.

The District Court explained that the DSHEA called for a de novo examination of the evidence in all proceedings, but found it unnecessary to conduct that examination in light of the FDA's violation of its statutory mandate. App. 34. The Court further held that the FDA could not claim *Chevron* deference because DSHEA did not contain the same explicit warrant to run a risk-benefit analysis that the FDCA uses to determine whether a device is safe and effective, 21 U.S.C. § 360c(a)(2) (2006). Rather, the District Court held that the major purpose of DSHEA was to "harmonize" the treatment of dietary supplements with that of foods in the pre-existing Act. App. 37-39.

4. The Decision of the Tenth Circuit

The Tenth Circuit unanimously reversed the decision below. *Nutraceutical Corp. v. Von Eschenbach*, 459 F.3d 1033 (10th Cir. 2006). The Tenth Circuit noted the high frequency of AERs that prompted the FDA to form its Food Advisory Committee in 1996 and to commission Dr. Inchiosa's 1999 letters comparing dietary ephedrine alkaloids with the drugs epinephrine and ephedrine. App. 6. It thereafter noted and endorsed the FDA's conclusion

that "[t]he best clinical evidence for a benefit . . . supports only a modest short-term weight loss, insufficient to positively affect cardiovascular risk factors or health conditions associated with being overweight or obese. Final Rule at 6789." App. 6-7. It then held that the de novo standard of review applies only when the District Court "decides" a particular matter, not when it just "reviews" it, and thus limited de novo review to enforcement actions, thereby allowing the use of *Chevron* deference to the agency. App. 8. Notwithstanding this earlier determination, the Tenth Circuit applied the canon of surplusage to conclude that by using the words "or unreasonable risk" Congress "unambiguously required the FDA to conduct a risk-benefit analysis under DSHEA." App. 10. In support of that conclusion, it cited this Court's recent decision in *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005). App. 10-11. It then focused on the overriding purposes of protecting public health (which applies to the entire FDCA) to conclude that DSHEA should receive a "liberal construction" on remedial issues, especially since the government has to bear the cost of assembling the information needed to run its risk-benefit analysis. App. 11-12. It then held that the District Court had "erred by conflating the terms 'significant' and 'unreasonable,' thereby rendering 'unreasonable' superfluous." App. 13. The court upheld FDA's determination on the ground that "the FDA found that the weight loss and other health benefits possible from the use of EDS were dwarfed by the potential long-term harm to user's cardiovascular system." App. 14. It supported this conclusion by citing to "multiple studies which demonstrated that EDS raise blood pressure and increase heart rate." App. 17 n.11. The Tenth Circuit also noted that the 1996 Food Advisory Committee echoed

the conclusion that "[t]here was, apparently, not enough evidence to support the conclusion that there is a safe level of intake for EDS." App. 19. It then echoed the FDA's decision to give "more weight to benefits that improve health outcomes, especially in the long term, than to benefits that are temporary or rely on subjective measures such as feeling or looking better." App. 20; App. 96 (Final Rule). That court therefore concluded that "the FDA correctly followed the congressional directive to analyze the risks and benefits of EDS in determining that there is no dosage level of EDS acceptable in the market," App. 20, and reversed the decision below, entering summary judgment for the appellants.

REASONS FOR GRANTING THE PETITION

A. The Tenth Circuit's Reading of DSHEA Wholly Ignores the Congressional Compromise Adopted for Dealing with Dietary Supplements, One that Imposes on FDA the Burden to Show that a Dietary Supplement Presents a Significant or Unreasonable Risk of Illness or Injury under Recommended or Suggested Conditions of Use.

This case offers a key test of whether the FDA will be required to observe the statutory boundary between foods and drugs critical to the organization of the FDCA. Foods need only be safe to be marketed, and no proof of benefit is required. See 21 U.S.C. § 342. By contrast, drugs (defined principally as articles intended for use in the treatment of disease, 21 U.S.C. § 321(g)(1)(b)) must be proven safe and efficacious to be marketed, so that proof of efficacy is always required. 21 U.S.C. §§ 321(p), 355. Both the statute

and the legislative history (S. Rep. No. 103-410) insist that all dietary supplements be treated as foods, not drugs. "[Section 321(ff)] is intended to be explicit about a point that ought to be clear . . . : a product intended . . . to supplement the diet with any . . . herb . . . is subject to regulation as a food and not as a drug." S. Rep. No. 103-410 at 19.

The FDCA's treatment of dietary supplements represents a carefully crafted compromise between those who wish to subject these products to minimal, if any, regulation and those who want to subject them to the exhaustive procedures normally associated with prescription drugs. Derived from substances consumed as foods, typically not man-made as are most drugs, and intended to supplement the daily diet, not to provide therapeutic benefit, dietary supplements have thus been classified as foods, not as drugs. The plain and intended meaning of the FDCA's Adulterated Food section compels FDA to obtain dose dependent proof of risk before it bans dietary supplements from the market. By its massive statutory sleight of hand, the Tenth Circuit has subjected EDS, a statutory foodstuff, to the identical and arduous risk-benefit standard used to determine whether drugs intended to treat disease may enter the market. In so doing it has done violence to the basic statutory scheme that seeks to keep distinct boundaries between these two categories.

Against this backdrop, the Tenth Circuit decision has thus engendered instability in food and dietary supplement markets, making it impossible for producers and consumers alike to predict with confidence that their products will stay on the market. The fundamental principle that governs both the science and the law of adulteration is that dose determines toxicity. Unless this Court

takes this case, the FDA, armed with the Tenth Circuit decision, can remove products from the market by showing that any use or abuse of a dietary supplement may cause harm without even attempting to show what the DSHEA mandates: evidence of harmful effects at the dose levels recommended or suggested in labeling.

Remarkably the District Court and the Tenth Circuit each held the Adulterated Food section unambiguous under *Chevron* Step 1. To our knowledge this is the only case in which two federal courts have applied that test to reach opposite views of statutory meaning and opposite results on an identical record. A close examination of the novel procedural and substantive issues shows that the District Court was faithful to the statutory text, structure, and purpose, but the Tenth Circuit was not.

B. The Tenth Circuit's Reading of DSHEA Disregards the Explicit Procedural Protections that the Act Confers on the Manufacturers of Dietary Supplements

On the central question of what is required of the FDA, the District Court took the sensible position that the statute required "that the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated." App. 38. In applying this standard, the District Court concluded that "the conditions of use suggested or recommended in labeling" meant that the FDA, as agent of the United States, had to make out the case of adulteration at that particular level, i.e., 10 mgs or less per day in the petitioners' case. That conclusion is surely correct because the whole point of section 342(f)(1)(A)(i) is to rule out of consideration all instances of *excess* product use in the FDA's evaluation. It is for that

reason that section 342(f)(1)(A)(ii) insists that the determination of adulteration be made for "*ordinary* conditions of use" when the label contains no suggested or recommended amounts. Abusive users may present a serious public health risk, but the remedy for that does not lie in removing every dose of the abused product from the marketplace. The only proper statutory result in this case is for the FDA to collect field data or run tests that determine the dose level at which EDS "presents a significant or unreasonable risk of illness or injury," i.e., to do what the statute commands, running tests of EDS at the dosages suggested or recommended and determining whether *that* use yields toxicity. No practical reason prevented the FDA from running tests or studies that fully complied with the statutory mandate. In dealing with the approval that it makes of drugs over which it has the power of premarket approval, the FDA never draws the inference that a product found safe and effective at one dosage level is safe and effective at all dosage levels. Instead, it demands that the drug companies run clinical trials that are dosage specific, precisely because it understands toxicity to be dose dependent. 21 U.S.C. § 342(f)(1)(A)(i); see also, S. Rep. No. 103-410 at 36. Nonetheless, in the area of foodstuffs FDA is now prepared to allow itself the benefit of these slapdash procedures and unsupported inferences in the teeth of an explicit statutory mandate to the contrary.

Consider the interpretive techniques that the Tenth Circuit used to stray far from the explicit and clear provisions of the DSHEA. At the outset the Tenth Circuit rejected the view that section 342(f)(1) placed the burden of proof on the United States in a de novo proceeding in the District Court. The statutory language, however,

is plain on the point: "In any proceeding under this subparagraph, the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated. The court shall decide any issue under this paragraph on a de novo basis." 21 U.S.C. § 342(f). In reading this provision, the Tenth Circuit adopted the strained and improbable view that the word "decide" in the above-quoted statutory sentence did not cover cases in which the District Court was called upon to "review" FDA rulemaking decisions, but only decisions arising from FDA enforcement actions: "Reading the statute as a whole, it is clear that the de novo standard applies when courts 'decide' matters rather than when they 'review' administrative decisions. As such, it is appropriate to limit the de novo standard of review, which affords the FDA no deference, to enforcement proceedings." App. 8.

With all due respect, this crabbed reading of the statute makes no sense. The statute is clear that it applies "in any proceedings," which includes on its face the Petitioners' challenge to the government's administrative rule. In addition, the term "decide" surely encompasses the narrower term "review." Structurally, moreover, the distinction the Tenth Circuit drew between administrative decisions and enforcement actions would allow the FDA to escape de novo review at its discretion. The reference to a "de novo basis," as applied to "any issue," unmistakably requires that the FDA build up its case from scratch in the District Court, without the benefit of any presumption that effectively undercuts its statutory burden of proof.

Having gutted the explicit procedural protections built into Section 342(f), the Tenth Circuit then proceeds to finesse the burden of proof requirement by reading out of the statute the requirement that the FDA bear the burden

of proof on "each element" of the case, of which the dosage level element is paramount. Thus the FDA gathered all sorts of evidence directed to the use of EDS generally, which did not distinguish, as DSHEA requires, between proper and excessive use. Pointedly, however, FDA did not seek to gather or examine *any* direct evidence of the effect of EDS at the 10 mg or lower recommended daily dose levels. On the strength of this impermissible procedure, the Tenth Circuit claimed that the FDA had actually found that the recommended or suggested usage of EDS posed an unreasonable risk of illness or injury. But the evidence that it quotes shows no such thing. Rather, the FDA, and all the data on which it relied, only stated that there was *insufficient evidence* on which to reach the conclusion that EDS was safe at every level of exposure, not that there was *sufficient evidence* on which to conclude that EDS was unsafe at 10 mg or less daily dose levels. Look again at the evasive way in which the Tenth Circuit and FDA put the case:

> Dr. Inchiosa . . . states that he cannot determine a safe level of EDS intake. This sentiment is echoed throughout the transcript of the [1996 Food Advisory Committee]. Several of the meeting's attendees made comments that a safe level could not be determined. There was, apparently, not enough evidence to support the conclusion that there is a safe level of intake for EDS.

App. 19. The proper question under the statute is not whether there is no evidence of a safe dose but whether there is credible evidence of risk at a particular dose, whereupon adulteration may be found at that dose and above but not below that dose. The Tenth Circuit's adoption of the FDA's studied phraseology can only be read as saying that the Petitioner has not yet come up with

evidence that persuades this group of experts that the use of 10 mgs or less of EDS is safe, so therefore FDA is entitled to presume the product unsafe until that speculative supposition is disproven, effectively reversing the burden of proof the statute places squarely on FDA. 21 U.S.C. § 342(f). If FDA may rest upon the absence of evidence (on a determination that evidence of a safe level of EDS does not exist), then it effectively has no burden of proof at all. A solemn declaration of not enough evidence to determine a safe level is not the same as a determination that harm exists at a certain dose level and above. The artful presentation of *all* the evidence that the FDA puts in the record admits *on its face* that the FDA has not been able to come up with a single shred of evidence out of an over 300,000 page administrative record that allows it to discharge its statutory duty to prove that EDS counts as an adulterated product at daily dose levels of 10 mgs or less. The District Court was right to hold FDA's feet to the fire on the central requirement of Section 342(f)(1).

Nonetheless, the FDA and the Tenth Circuit seek to wiggle out from that result by insisting that the overall objective of promoting public health requires the adoption of a "liberal construction" when the FDA seeks to introduce remedial measures. App. 11. It is, however, a common canon of statutory construction that general attitudes that apply to an entire statute must give way to specific evidence in the legislative history that applies to the particular provisions at hand. *Board of Governors of the Federal Reserve System v. Dimension Financial Corp.*, 474 U.S. 361, 373-74 (1986). On this score, the record is clear. As the Tenth Circuit recognized, "[i]t is true DSHEA was enacted to alleviate the regulatory burdens on the dietary supplement industry, allowing consumers greater access to safe dietary supplements in order to promote greater

wellness among the American population." See generally Dietary Supplement Health and Education Act, Pub. L. No. 103-417, § 2 (1994)," as quoted in *Pharmanex v. Shalala*, 221 F.3d 1151, 1158-59 (10th Cir. 2000).

Indeed, the record is replete with further evidence that Congress had an abiding suspicion of FDA overreaching when it adopted DSHEA, evidence the Tenth Circuit ignored. Congress endeavored to "assure [that] citizens have continued access to dietary supplements and information about their benefits," S. Rep. No. 103-410 at 17, and explained that the amendment would "correct [FDA's] abuse[s] by rationalizing the treatment of dietary supplements according to the pattern of the existing statute, and in conformity with the original congressional intent." S. Rep. No. 103-410 at 22. In addition the amendment "establish[ed] in law the rule that in any proceeding against a dietary supplement, the government bears the burden of proof of showing that a dietary supplement is adulterated." S. Rep. No. 103-410 at 22. Congress intended that "a safety finding" never be "entered against a supplement based upon a dosage not recommended to consumers in the labeling," S. Rep. No. 103-410 at 36, thus reinforcing the plain meaning of the statute that dose determination of toxicity is central. The DSHEA also deemed dietary supplements "food[s] within the meaning of this Act" in 21 U.S.C. § 321(ff). None of these passages supports the supposed canon of liberal construction promulgated by the Tenth Circuit. To the contrary, the full legislative history perfectly complements the explicit statutory language. In light of the perfect concordance between the text and legislative history, it is indefensible to disregard or misread each and every one of the procedural protections that DSHEA affords to the petitioners,

yet that is precisely what the Tenth Circuit has done. The FDA may surely be aggressive in collecting evidence to prove adulteration under DSHEA, but the agency cannot dispense with meeting specific statutory requirements in its zeal to advance the public good.

C. The Tenth Circuit Decision Improperly Allows the FDA to Conduct a Risk-Benefit Analysis of Foodstuffs under Procedures that the FDCA Reserves Exclusively for Drugs.

The gist of the Tenth Circuit decision is its finding "that Congress unambiguously required the FDA to conduct a risk-benefit analysis under DSHEA." App. 10. As explained *supra*, the key structural feature of the FDCA is the establishment of separate regulatory regimes for foods and dietary ingredients, on the one hand, and drugs, on the other. In the teeth of this overarching principle, the Tenth Circuit accepted the FDA's contention that the words "unreasonable risk" required use of a risk-benefit analysis expropriated from the New Drugs section of the FDCA. App. 10-11. Both the FDA and the Tenth Circuit took the view that the phrase "unreasonable risk" should be read in isolation from all other terms in the statutory sentence, to avoid treating the words as "surplusage," which would render the phrase "superfluous language." App. 13. Accordingly, the Tenth Circuit held the term "unreasonable risk" required a risk-benefit comparison as prescribed in the New Drugs section of the FDCA, 21 U.S.C. § 355. App. 10-11.

The first objection to this approach arises because the Tenth Circuit has violated the holding of this Court that the surplusage canon not be used to interpret the law

contrary to congressional intent. *Scheidler v. National Org. for Women, Inc.*, 126 S.Ct. 1264, 1273 (2006) ("Those canons are tools designed to help courts better determine what Congress intended, not to lead courts to interpret the law contrary to that intent"). But even under the surplusage canon, the Tenth Circuit's decision fails because it has not satisfied the statutory requirement that adulteration be determined based on recommended or suggested dosages in labeling. The surplusage canon hardly requires the FDA to introduce through the back door a fundamental regime change whereby dietary supplements are now evaluated under the standards reserved for drugs in the FDCA with the FDA bearing (an attenuated) burden of proof.

The Tenth Circuit has ruled out the possibility of a simpler reading, one consistent with the plain language of the statute and the legislative intent. "Unreasonable" need not beget a meaning independent of all other words in the statutory sentence nor does it require consideration of health benefit when no reference to a comparison of risk with benefit exists in the Adulterated Food section or in the legislative history pertaining to that section. "Unreasonable" does not require abandonment of the central principle of adulteration law, the Paracelsian axiom that dose determines toxicity. Within the meaning of the statute, a risk becomes "unreasonable" at a dose level that causes illness or injury. A risk becomes "significant" based on the degree of illness or injury experienced (e.g., a tumor as opposed to a headache). The term "or" does not carry a disjunctive meaning, such that FDA is at liberty to ignore "significant" risk in finding adulteration. Rather, each term independently modifies the noun "risk" and must be

interpreted. Harmonized with the food subparts of Section 342, a "significant or unreasonable risk" is one that causes illness or injury at a particular dose level (and above) that cannot be mitigated through modification of labeling but is a characteristic response experienced by users to the dose recommended, suggested, or ordinarily consumed. Moreover, "unreasonable" in the dietary ingredient subsection of the Adulterated Food section does not invite a construction of the FDCA that supports the bizarre distinction that defines a food containing 15 to 30 mg or more of a dietary ingredient exempt from the holding of adulteration but declares a dietary supplement containing 10 mg or less of the same dietary ingredient adulterated and banned from the market. Congress intended that the dietary ingredient subsection be *harmonized* with the pre-existing statute, S. Rep. No. 103-410 at 21, not interpreted to create a separate regime in conflict with the old. The FDA's view upheld by the Tenth Circuit is clearly incorrect because it exempts all ephedrine alkaloid-containing foods, including ephedra tea (having ephedrine alkaloids per serving in concentrations greater by far than the 10 mg per daily dose in the petitioners' dietary supplements). Indeed, the herb used in ephedra tea is precisely the same as the herb used in Petitioners' dietary supplement (raw crushed ephedra sinica), differing only in the amount of ephedrine alkaloids delivered (15 to 30 mg or more from the tea per serving compared to 10 mg or less mg from the capsule per daily dose). DSHEA contains no intimation that Congress has authorized an absurd reading of the Adulterated Food section, one that construes a single, uniform statutory section to yield an internally inconsistent result, against the statutory construction requirements of this Court. See

FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 133 (2000).

To bolster its weak textual argument on "unreasonable risk," the Tenth Circuit invoked the decision in *Merck KGaA v. Integra-Life Sciences I, Ltd.*, 545 U.S. 193 (2005) for the proposition that the words "unreasonable risk" in 21 U.S.C. § 342(f)(1) "involves a comparison of the risks and the benefits. . . ." But in making this leap the Tenth Circuit ignored its own injunction to place statutory language in its larger context. The particular section (21 U.S.C. § 355(i)(3)(B)(I)) quoted in *Merck KGaA* itself had nothing to do with the evaluation of either foods or drugs under the FDCA, but exclusively concerned the various protections that the Hatch-Waxman Act gave to potential drug patent infringers that were engaged in medical research with an eye to obtaining FDA marketing approval.

Finally, the Tenth Circuit's reading is wholly inconsistent with other fundamental provisions of the FDCA. As the District Court rightly explained, 21 U.S.C. § 360c(a)(2), governing medical devices, contains an explicit provision whereby, "the safety and effectiveness of a device are to be determined [by]. . . . (C) weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use." The District Court then concluded pointedly and correctly, "[t]he DSHEA contains no such provision." App. 37. In other cases, courts have held that the statute should be evaluated "'as a symmetrical and coherent regulatory scheme' and 'fit, if possible, all parts into a harmonious whole.'" *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000). That proposition is applicable in this case and should have caused the Tenth Circuit to enjoin FDA from overstepping

the boundaries of the relevant statutory command. FDA had no warrant for analyzing foods within the Adulterated Food section as if they were drugs in the New Drugs section. In so doing, FDA consciously departed from the statutory scheme that intentionally regulates foods for use in the diet differently from drugs for use in the treatment of disease.

The FDA has fundamentally altered food adulteration law in America without authorization from Congress. It has rewritten that law, and the Tenth Circuit has condoned that rewrite and the usurpation of legislative power effected by it. FDA has declined to make any finding that EDS in dose amounts of 10 mgs or less create a "significant" risk of any kind. Yet in the face of that yawning gap, it has undertaken a purported risk-benefit analysis that fails to give accurate weight to either the risks or the benefits. On the risk side, the FDA has not made *any* estimate of the relevant health costs of the slight risks that it perceived, *but did not prove*, for EDS dosages of 10 mgs or less. At the same time, the FDA arbitrarily truncated its analysis of the benefit side of the equation by looking solely at *clinically proven* health benefits of EDS, which, ironically, are appropriate to consider only for drugs, not foods. (EDS could not be sold as a drug because it does not have the requisite FDA approvals.) The FDA thus overlooked consumer preferences that constitute an indispensable part of any economic cost-benefit analysis.

Consequently, the FDA's risk-benefit test is stacked against finding any benefit capable of overcoming even slight risk that attaches to the use of every substance. (Without dose dependency, risk constitutes a ubiquitous condition of all things ingested, even water). Under its new risk-benefit test for adulteration, FDA has eliminated

all of the statutory constraints on the exercise of its authority to remove dietary supplements from the market; it is now free to remove any dietary ingredient because every one arguably meets its new criteria: every one presents a perceptible risk of illness or injury *at some dose level* of ingestion, and every one may be subjectively viewed as conveying a health benefit insufficiently weighty to counterbalance perceived risk.

The Tenth Circuit further errs when it notes with approval that "[i]n determining that EDS pose an 'unreasonable risk of illness or injury,' the FDA found that the weight loss and other health benefits possible from the use of EDS were dwarfed by the potential long-term harm to the user's cardiovascular system." App. 14. That proposition is not credible. FDA never evaluated the effects of 10 mg or less EDS in any clinical trial of actual users; it has no data on the effect of those dose levels on the cardiovascular system of users. Indeed, it has no record evidence of any "long-term harm to the user's cardiovascular system" from ingestion of EDS. Moreover, there is simply no way in which the full range of benefits could be "dwarfed by the potential long-term harm" when the FDA has refused to make any finding that the harms in question are significant. The FDA has not once studied the effects of long-term ingestion of 10 mgs or less of ephedrine alkaloids. Instead it relied on the "validity" of a *non sequitur*: that the absence of evidence proving safety is the same as the presence of evidence proving harm. Quite simply, the FDA has smuggled a finding of significant risk into its unbalanced risk-benefit analysis. Without an unarticulated assumption that significant risk exists, how could FDA say that the full set of health and nonhealth benefits of EDS

are dwarfed by a speculative, unproven and, in any event, insignificant long-term risk of harm?

In sum, if the FDA is allowed to conduct future analyses of dietary supplements under the skewed test that it has adopted and the Tenth Circuit has upheld, then the congressional compromise that defines separate regimes for foods and drugs no longer holds true in the food adulteration context. Rather, the FDA may henceforth draw inferences about the risks of dietary supplements at any dose level whatsoever, in the face of the statutory requirement that it run its evaluation at the recommended or suggested levels of use. It may henceforth evade its burden of proof by relying on unpeer-reviewed, solicited opinion letters that present untested models that extrapolate from results of tests conducted on different substances (drugs) intravenously injected and presume those results the same for dietary ingredients orally ingested. Under the Tenth Circuit's decision, FDA may now insist that infinitesimal risks are unreasonable, magnifying them beyond the record evidence, as it has done in Nutraceutical's case, and then conduct a statutorily unauthorized benefit comparison that ignores all non-health benefits and subjectively deems virtually all health benefits insufficiently weighty to counterbalance perceived risks. Indeed, significant and clinically proven health benefits, presumably the kind that might be viewed by FDA as sufficiently weighty, cannot be demonstrated because intent to produce therapeutic benefits defines a drug and is impermissible for supplements.

In short, the FDA has nullified the bedrock of adulteration law, that dose determines toxicity. It has negated the fundamental requirement that FDA prove a dietary ingredient itself, rather than a surrogate substance, i.e., a

drug, a significant risk before banning the ingredient from the market. Without statutory authorization and against the plain and intended meaning of Congress, FDA has superimposed on the Adulterated Food section a drug risk-benefit standard, eliminating the essential divide between foods and drugs created by the FDCA and rendering the critically important Adulterated Food section internally inconsistent and irrational. That rewrite of the law is causing instability in food and supplement markets. Lawless behavior by agencies in defiance of their enabling statutes should never be tolerated when the means are at hand to correct that behavior.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted,

NUTRACEUTICAL CORPORATION
and SOLARAY INC.

By its counsel:

JONATHAN W. EMORD
Counsel of Record
EMORD & ASSOCIATES, P.C.
1800 Alexander Bell Drive
Suite 200
Reston, VA 20191
(202) 466-6937

RICHARD A. EPSTEIN
111 East 60th Street
Chicago, IL 60637
(773) 702-9563

459 F.3d 1033

PUBLISH

UNITED STATES COURT OF APPEALS

TENTH CIRCUIT

NUTRACEUTICAL CORPORATION; SOLARAY, INC.,

Plaintiffs-Appellees,

v.

ANDREW VON ESCHENBACH, Acting Commissioner, U.S. Food and Drug Administration; UNITED STATES FOOD AND DRUG ADMINISTRATION; MICHAEL O. LEAVITT, Secretary of the Department of Health and Human Services; DEPARTMENT OF HEALTH AND HUMAN SERVICES; UNITED STATES OF AMERICA,

Defendants-Appellants.

No. 05-4151

(Filed Aug. 17, 2006)

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF UTAH
(D.C. No. 2:04-CV-00409-TC)

Christine N. Kohl, Attorney (Peter D. Keisler, Assistant Attorney General, Paul M. Warner, United States Attorney, Jeffrey Bucholtz, Deputy Assistant Attorney General,

and Douglas N. Letter, Attorney, Department of Justice, Washington, D.C., and Paula M. Stannard, Acting General Counsel, Sheldon T. Bradshaw, Associate General Counsel, Eric M. Blumberg, Deputy Chief Counsel, and Claudia J. Zuckerman, Associate Chief Counsel, Office of General Counsel, U.S. Department of Health & Human Services, Food and Drug Division, Rockville, Maryland, with her on the briefs), for Defendants-Appellants.

Jonathan W. Emord (Andrea G. Ferrenz with him on the brief), Emord & Associates, P.C., Reston, Virginia, for Plaintiffs-Appellees.

Before **KELLY**, **TYMKOVICH**, Circuit Judges and **EAGAN**,* District Judge.

EAGAN, District Judge.

Defendants-appellants, Andrew von Eschenbach, M.D., Acting Commissioner of the U.S. Food and Drug Administration, the United States Food and Drug Administration ("FDA" or "the agency"), Michael O. Leavitt, Secretary of the Department of Health and Human Services, the Department of Health and Human Services, and the United States, appeal from a judgment of the district court denying their motion for summary judgment and granting the cross-motion of plaintiffs-appellees for summary judgment. *Nutraceutical Corp. v. Crawford,* 364 F. Supp. 2d 1310 (D. Utah 2005). Plaintiffs-appellees, Nutraceutical Corporation and its wholly-owned subsidiary, Solaray Corporation (collectively, "Nutraceutical"),

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* The Honorable Claire V. Eagan, District Judge, United States District Court for the Northern District of Oklahoma, sitting by designation.

manufacture and sell Ephedra, a product containing ephedrine-alkaloid dietary supplements ("EDS"). In 2004, the FDA issued a regulation which banned all EDS sales in the United States market. Nutraceutical brought this action challenging the regulation as unlawful. The district court agreed with Nutraceutical. *Id.* at 1321. Our jurisdiction arises under 28 U.S.C. § 1291, and we reverse.

Background

In its published decision, the district court determined that the risk-benefit analysis employed by the FDA to support an EDS ban was contrary to the intent of Congress and that the FDA had failed to prove by a preponderance of the evidence that EDS pose an unreasonable risk of illness or injury at 10 milligrams ("mg") or less a day. *Nutraceutical,* 364 F. Supp. 2d 1310. It accordingly entered summary judgment in favor of Nutraceutical, enjoined the FDA from enforcing its proscription against Nutraceutical for the sale of products with a recommended daily dosage of 10 mg or less of EDS,[1] and remanded to the FDA for new rule-making.

The issues raised by this appeal are: (1) whether the FDA correctly interpreted the relevant statute to require a risk-benefit analysis in determining if a dietary supplement presents an "unreasonable risk of illness or injury"; and (2) whether the FDA satisfied its burden of proving that dietary supplements containing EDS present an

[1] To the extent that we recognize Nutraceutical's product as recommending less than 10 mg of ephedrine alkaloids per day, Nutraceutical's Motion to Correct Oral Argument Record, filed on May 11, 2006, is granted.

unreasonable risk of illness or injury when doses of 10 mg or less per day are suggested or recommended in labeling.

Nutraceutical alleges that the FDA lacked statutory authority to promulgate and enforce a ban of all EDS. The FDA argues that it acted pursuant to the broad authority delegated to it by the Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301, *et seq.*, to regulate dietary supplements for safety. The FDCA provides the FDA with broad authority to regulate food, drug, and dietary supplement products in order to ensure public health and safety. *Id.* In 1994, Congress amended the FDCA with the Dietary Supplement Health and Education Act ("DSHEA"), Pub. L. No. 103-417, 108 Stat. 4325 (1994). Under DSHEA, the FDA regulates vitamins, minerals, herbs, amino acids, and other dietary substances. Dietary supplements are generally regulated in a manner similar to food and the FDA is authorized to prevent adulterated products from entering the market. *See* 21 U.S.C. § 331(a), (b), (c), (k) (adulteration and distribution of adulterated food are prohibited acts). Congress declared that a dietary supplement is "adulterated":

> If it is a dietary supplement or contains a dietary ingredient that –
>
> (A) presents a significant or unreasonable risk of illness or injury under –
>
> > (i) conditions of use recommended or suggested in labeling, or
> >
> > (ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use; . . .

21 U.S.C. § 342(f)(1). The FDA argues that EDS are adulterated and points to the "unreasonable risk of illness or injury" provision of DSHEA as the primary source of statutory authority for its EDS ban. 21 U.S.C. § 342(f)(1)(A).

Ephedrine alkaloids are a class of structurally-related chemical stimulants that occur naturally in some botanicals. In the 1980s and 1990s, manufacturers promoted the sale of EDS for weight loss and athletic performance enhancement. In the 1990s, the FDA received numerous Adverse Event Reports ("AERs") which documented harmful side effects, including heart attacks, strokes, seizures, and death, associated with EDS intake.[2] Based on the circumstantial evidence of the AERs, the FDA began to investigate the effects of EDS. The investigation included a literature review of scientific studies and a Food Advisory Committee on Dietary Supplements Containing Ephedrine Alkaloids Meeting held on August 26-27, 1996 ("1996 Food Advisory Committee"). In 1997, the agency proposed a regulation which would have required specific warnings and established a dosage regimen. 62 Fed. Reg. 30,678 (June 4, 1997).

The FDA's 1997 proposed regulation of EDS faced substantial opposition, including from the General Accounting Office ("GAO"). The GAO determined that the FDA had not been thorough in its investigation and requested further research. *See* GAO, *Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine*

[2] The FDA established the MedWatch program to monitor AERs associated with nutritional products, including dietary supplements. This program relies on voluntary reporting from public health agencies, health professionals, and consumers. *See* FDA MedWatch Home Page, http://www.fda.gov/medwatch/.

Alkaloids 11 (1999). Responding to the GAO's concerns, the FDA withdrew the 1997 proposed regulation. 65 Fed. Reg. 17,474 (Apr. 3, 2000).

The FDA continued to receive AERs and compile scientific literature regarding EDS. Given the fact that dietary supplement manufacturers are not required to submit scientific data on their products, the body of scientific literature on EDS was limited. Among the studies on which the FDA relied was a report commissioned by the National Institutes of Health. To further supplement the record, the agency hired Mario A. Inchiosa, Jr., Ph.D.,[3] to conduct further research on the health effects of EDS in 1999. During the public notice and comment period, Nutraceutical submitted to the FDA several requests for an exemption of low-dosage EDS, to no avail. The administrative record grew to over 130,000 pages, approximately 19,000 AERs were collected,[4] and extensive public notice and comment resulted in over 48,000 comments.

After seven years of investigating EDS, the FDA adopted a regulation which banned EDS at all dosage levels from the national market. Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, 69 Fed. Reg. 6788 (Feb. 11, 2004) ("Final Rule"). In the Final Rule, the FDA concluded that "[t]he best clinical

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[3] Professor of Pharmacology, New York Medical College.

[4] The AERs which were voluntarily submitted to the FDA were supplemented with 16,000 complaints received by Metabolife, one of the largest distributors of EDS. 364 F. Supp. 2d at 1315; *see* GAO, *Dietary Supplements: Review of Health-Related Call Records for Users of Metabolife 356* (GAO-03-494) (2003).

evidence for a benefit . . . supports only a modest short-term weight loss, insufficient to positively affect cardiovascular risk factors or health conditions associated with being overweight or obese." *Id.* at 6789. Based on this risk-benefit analysis, the FDA determined that all EDS present an "unreasonable risk of illness or injury" under all ordinary or recommended conditions of use. *Id.* at 6788. As such, the Final Rule classified EDS adulterated within the meaning of DSHEA.

The district court held that "the FDA's requirement that EDS demonstrate a benefit is contrary to the clear intent of Congress" and found the agency's definition of "unreasonable" as entailing a risk-benefit analysis to be improper. 364 F. Supp. 2d 1310, 1319. The district court also found that the FDA failed "to prove by a preponderance of the evidence that a dosage of 10 mg or less of ephedrine alkaloids presents a significant or unreasonable risk of illness or injury." *Id.* at 1321. Based on these findings, the district court granted summary judgment for plaintiffs and denied summary judgment for defendants.

Discussion

Standard of Review

The district court's conclusions as to whether the FDA had acted pursuant to congressionally delegated authority in promulgating a rule is reviewed *de novo.* However, the parties dispute the appropriate standard of review of the administrative decision. DSHEA provides that: "The court shall decide any issue under this paragraph on a de novo basis." 21 U.S.C. § 342(f). The district court did "not reach the question of whether the FDA's statutory construction should be reviewed *de novo.*" 364 F. Supp. 2d at 1317. In

the interest of clarity and consistency, we now reach this question.

Courts are to review agency actions under DSHEA using the "traditional tools of statutory construction." *Pharmanex v. Shalala,* 221 F.3d 1151, 1154 (10th Cir. 2000). The *de novo* standard, under section 342(f), applies to enforcement actions by the United States against manufacturers of dietary supplements. Such enforcement actions may result in imprisonment or monetary fines. 21 U.S.C. § 333; *see United States v. Park,* 421 U.S. 658 (1975). Reading the statute as a whole, it is clear that the *de novo* standard applies when courts "decide" matters rather than when they "review" administrative decisions. As such, it is appropriate to limit the *de novo* standard of review, which affords the FDA no deference, to enforcement proceedings. Challenges by private parties to FDA rules promulgated under DSHEA are reviewed pursuant to the Administrative Procedure Act ("APA"), 5 U.S.C. § 706, and "the normal rules for judicial deference regarding agency action apply." *NVE, Inc. v. HHS,* 436 F.3d 182, 196 (3rd Cir. 2006). "Had Congress intended to supplant the well-established procedures for APA challenges, it would have been clearer about its objective." *Id.* at 194.

Chevron Analysis

A court reviewing the FDA's construction of the FDCA must determine: whether Congress has directly spoken to precise question at issue; and if not, then whether agency's construction of statute is permissible one. *Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.,* 467 U.S. 837, 842-43 (1984). In reviewing the FDA's interpretation of DSHEA under *Chevron,* we ask two questions:

> First, always, is the question whether Congress has directly spoken to the precise question at issue. If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress [*Chevron* step 1]. But if the statute is silent or ambiguous with respect to the specific issue, the question for the court is whether the agency's answer is based on a permissible construction of the statute. If Congress has explicitly or implicitly delegated authority to an agency, legislative regulations are given controlling weight unless they are arbitrary, capricious, or manifestly contrary to the statute [*Chevron* step 2].

Seneca-Cayuga Tribe of Oklahoma v. National Indian Gaming Com'n, 327 F.3d 1019, 1037 (10th Cir. 2003) (citations omitted).

The APA reflects the principles of *Chevron* and "provides that agency action must be set aside if the action was 'arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law' or if the action failed to meet statutory, procedural, or constitutional requirements." *Valley Cmty. Pres. Comm'n v. Mineta,* 373 F.3d 1078, 1084 (10th Cir. 2004) (internal quotation omitted) (citing 5 U.S.C. § 706). "When we review an agency's decision under the arbitrary, capricious or abuse of discretion standard [of the APA], our review is narrow and deferential; we must uphold the agency's action if it has articulated a rational basis for the decision and has considered relevant factors." *Slingluff v. Occupational Safety & Health Review Comm'n,* 425 F.3d 861, 866 (10th Cir. 2005) (citing *Mountain Side Mobile Estates P'ship v. Sec'y of HUD,* 56 F.3d 1243, 1250 (10th Cir. 1995)). Under

the APA, regulations are presumed to be valid, and review is deferential to the government agency.

"Unreasonable Risk"

In this case, we must determine whether Congress unambiguously manifested its intent to restrict the FDA from weighing benefits when determining the risk posed by a dietary supplement. The district court was correct to proceed under *Chevron* step one in deciding the question of whether the FDA properly used a risk-benefit analysis in determining whether EDS pose an "unreasonable risk." *Chevron,* 467 U.S. at 843. We nevertheless reverse the district court after finding that Congress unambiguously required the FDA to conduct a risk-benefit analysis under DSHEA.

In 1994, Congress enacted DSHEA to clarify that dietary supplements, absent declarations promoting the supplements as drugs, would be regulated in a manner similar to food products. Accordingly, in the interest of public health, Congress imposed a duty on the FDA to keep adulterated dietary supplements off the market. 108 Stat. at 4326 (instructing the FDA to "take swift action against [dietary supplements] that are unsafe or adulterated."). DSHEA classifies a dietary supplement as adulterated if it "presents a significant or unreasonable risk of illness or injury." 21 U.S.C. § 342(f)(1). The FDA understood "[t]he plain meaning of 'unreasonable' . . . [to] connote [] comparison of the risks and benefits of the product." 69 Fed. Reg. 6788, 6823 (2004). We agree. The plain language of the statute directs the FDA to restrict distribution of dietary supplements which pose any risk that is unreasonable in light of its potential benefits. *See Merck*

KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193 (2005) (unanimously finding that "unreasonable risk," as used in another FDCA provision, 21 U.S.C. § 355(i)(3)(B)(I), "involves a comparison of the risks and the benefits. . . .").

Congress enacted DSHEA in an effort to improve public access to dietary supplements based on the belief that there may be a positive relationship between dietary supplement use, reduced health-care expenses, and disease prevention. *See Pharmanex,* 221 F.3d at 1158-59 ("It is true that DSHEA was enacted to alleviate the regulatory burdens on the dietary supplement industry, allowing consumers greater access to safe dietary supplements in order to promote greater wellness among the American population.") (citation omitted). The FDCA should not be read too restrictively but in manner consistent with the statute's overriding purpose to protect public health. *See* 21 U.S.C.A. § 301 *et seq.; United States v. Rx Depot, Inc.*, 438 F.3d 1052, 1061 (10th Cir. 2006) ("The FDCA's primary purpose is to protect the public health.") (citing *United States v. An Article of Drug . . . Bacto-Unidisk,* 394 U.S. 784, 798 (1969)). Accordingly, DSHEA should receive a liberal construction where the FDA has taken remedial steps in response to a perceived public health problem.

According to the district court, by injecting a risk-benefit analysis, the FDA required Nutraceutical to make a showing of the benefits of its product. However, at no time has the FDA required manufacturers of EDS to provide data on the benefits of their products. Rather, the FDA has assumed its responsibility of gathering data, soliciting comments, and conducting the risk-benefit

analysis.[5] Congress expressly placed the burden of proof on the government to determine whether a dietary supplement is adulterated. Accordingly, EDS were allowed to enter the market without findings of safety or effectiveness. The FDA did not impose a pre-market requirement for the sale of EDS. For example, Nutraceutical has been selling EDS since 1988. As dictated by the statutory scheme, the FDA assumed the duty of post-market surveillance and imposed the EDS ban following numerous AERs, public notice and comment, and significant scientific review. *See* 69 Fed. Reg. 6788. Based on the record, we disagree with the district court and find that the FDA did not shift the burden of proof to manufacturers. The risk-benefit analysis is conducted by, and at the expense of, the agency. *Id.* at 6798 ("the agency performs a risk/benefit analysis to ascertain whether the risks of the product outweigh its benefits."). Despite Nutraceutical's characterization of the process, the agency did not "require[] proof of a substantial benefit to counterbalance risk as a condition precedent to lawful sale of EDS." Appellee's Brief, at 5. The burden remains on the agency to show that risks associated with a dietary supplement outweigh benefits and are, therefore, unreasonable. Thus, a risk-benefit analysis

[5] The district court compared the language of DSHEA to the statutory language governing medical devices and drugs and concluded that, unlike manufacturers of medical devices and drugs, manufacturers of dietary supplements do not need to prove effectiveness prior to taking their product to market. 364 F. Supp. 2d at 1318 ("A brief look at the legislative history of the DSHEA indicates that Congress generally intended to harmonize the treatment of dietary supplements with that of foods when it added the dietary supplement subsection to the food adulteration provision."). The district court is correct. However, the district court confused effectiveness with safety. The FDA did not ban EDS for failing to deliver promised health gains or for ineffectiveness; the FDA banned EDS because they were determined to be unsafe.

does not undermine congressional intent by improperly shifting the burden of proof onto manufacturers of dietary supplements.

Under the rules of statutory construction, courts consider the whole act and evaluate terms in context. *Pharmanex,* 221 F.3d at 1154 ("we examine the statutory provision in context."). The rule against surplusage encourages courts to give meaning to every word used in a statute to realize congressional intent. In effect, this rule embodies the belief that Congress would not have included superfluous language. Thus, in DSHEA, an "unreasonable risk" has a meaning independent from a "significant risk." The plain meaning of a "significant risk" is a great danger. "Unreasonable risk" is a distinct term and requires more than evaluation of the significance of risk. "A risk could be significant but reasonable if the benefits were great enough to outweigh the risks." 69 Fed. Reg. at 6823. In other words, an "unreasonable risk" is relative to the circumstances; the potential risk is more "unreasonable" if the potential benefit is smaller. *See Castrignano v. E.R. Squibb & Sons, Inc.,* 900 F.2d 455, 459 (1st Cir. 1990) (upholding jury instructions which define "unreasonable" as the "balance between the expected beneficial effects of the [product] as opposed to its harmful effects, if any."). The district court erred by conflating the terms "significant" and "unreasonable," thereby rendering "unreasonable" superfluous. In contrast to "significant risk," "unreasonable risk" accounts for whether the benefits justify the risks. The use of "unreasonable" to qualify risk in addition to "significant" makes it clear that Congress intended to integrate a risk-benefit analysis in the former. Thus, because we find the statute is clear, we now review the FDA's absolute prohibition of EDS under the APA.

"Conditions of Use"

Under DSHEA, the government bears the burden of proof to show that, "under conditions of use recommended or suggested in labeling," a dietary supplement is adulterated. 21 U.S.C. § 342(f)(1)(A)(i). It is undisputed that the FDA must consider the dosage recommended in a dietary supplement's labeling when making an adulteration determination under section 342(f)(1)(A). The district court held that the FDA failed "to prove by a preponderance of the evidence that a dosage of 10 mg or less of ephedrine alkaloids presents a significant or unreasonable risk of illness or injury, [and] has failed to give effect to the dose-specific language of [] § 342(f)(1)(A)(I)." 364 F. Supp. 2d at 1321.

In determining that EDS pose an "unreasonable risk of illness or injury," the FDA found that the weight loss and other health benefits possible from the use of EDS were dwarfed by the potential long-term harm to the user's cardiovascular system. The agency went on to enact a complete ban on the product after making a finding that any amount of EDS had negative ramifications on the cardiovascular system and, based on the FDA's analysis, EDS provided no benefits so great as to justify such risk.

The preponderance of the evidence standard[6] requires the party with the burden of proof to support its position with the greater weight of the evidence. *See Metropolitan Stevedore Co. v. Rambo,* 521 U.S. 121, 137-38 n.9 (1997) (explaining that the preponderance of the evidence standard

[6] Congress did not prescribe the quantum of proof required under DSHEA. Accordingly, the standard traditionally applied in administrative cases, the preponderance of the evidence standard, governs. *See Steadman v. SEC,* 450 U.S. 91, 95, 102 (1981).

"simply requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence. . . .") (citation omitted); *Vesper Const. Co., Inc. v. Rain for Rent, Inc.*, 602 F.2d 238, 242 (10th Cir. 1979) ("by the greater weight of the evidence or, as it is sometimes called, the preponderance of the evidence."). The evidence relied on by the FDA to enact its ban of EDS covers over seven years of agency review, public notice and comment, peer-reviewed literature, and scientific data. It is the purview of the FDA to weigh the evidence, including the evidence submitted by Nutraceutical and other manufacturers during public notice and comment.

It is noteworthy that Nutraceutical relies on the 1999 GAO report to support its contention that the Final Rule lacks support. However, the GAO has since updated its findings and arrived at conclusions in support of the Final Rule. *See* GAO, *Dietary Supplements: Review of Health-Related Call Records for Users of Metabolife 356* (GAO-03-494) (2003). Based on scientific data and AERs, the GAO concluded that EDS pose a significant risk of cardiovascular and nervous system effects among consumers who are young to middle-aged. *See* GAO, *Dietary Supplements Containing Ephedra,* Testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives (July 23, 2003); 69 Fed. Reg. at 6818 (GAO found that AERs "were consistent with . . . the scientifically documented pharmacological and physiological effects of ephedrine alkoids.").

The FDA hired Dr. Inchiosa to study the effects of EDS on human health in 1999. Dr. Inchiosa used principles of

pharmacokinetics[7] to examine the effects of ingestion of EDS on the human cardiovascular system. Dr. Inchiosa found that ephedrine would be expected to produce the same adverse cardiovascular effects (increased heart rate and blood pressure) as a comparable dose of the pharmacologically-related drug, epinephrine,[8] and that, consequently, no dose of ephedrine can be considered safe. Nutraceutical raises objections to Dr. Inchiosa's study and methodology which it did not raise during the rulemaking.[9] Nutraceutical argues that Dr. Inchiosa's work is

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[7] A pharmacokinetic analysis is one which examines the bodily absorption, distribution, metabolism, and excretion of drugs. *Merriam Webster's Collegiate Dictionary* 871 (10th ed.1994).

[8] To reach his conclusions, Dr. Inchiosa relied on a peer-reviewed study of the effect of epinephrine in humans. William E. Clutter, et al., *Epinephrine Plasma Metabolic Clearance Rates and Physiologic Thresholds for Metabolic and Hemodynamic Actions in Man,* 66 J. Clin. Invest. 94 (July 1980). The Clutter study revealed significant increases in heart rate and blood pressure from epinephrine infusion at the rate of 0.5 μg/minute.

[9] Although Nutraceutical did not specifically object to Dr. Inchiosa's study and methodology during rulemaking, it did not thereby waive its objection. In a review of the decision of an administrative agency, a party waives its right to appeal an issue if it fails to object through comments or documents in the record. *New Mexico Environmental Imp. Div. v. Thomas,* 789 F.2d 825, 835 (10th Cir. 1986) (when agency solicited comments on the very issue being challenged, party "was obligated to make its record before the agency."); *American Frozen Food Institute v. Train,* 539 F.2d 107, 134 (D.C. Cir. 1976) ("What the industry failed to present to the Administrator during rulemaking procedures when specifically asked to comment cannot now be urged [as] a basis for invalidation [of the rule]."); *see also Fuel Safe Washington v. F.E.R.C.,* 389 F.3d 1313 (10th Cir. 2004); *Kennecott Copper Corp. v. E.P.A.,* 612 F.2d 1232, 1245 (10th Cir. 1979) ("it is well settled that industry must first utilize the opportunity for comment [on an agency regulation] before it may raise issues on appeal."). While Nutraceutical did not object to Dr. Inchiosa's study on the record, it did advance dissatisfaction with the scientific evidence relied on by the FDA during the rulemaking. Appellee's App., at 159-60 ("Nutraceutical submits

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irrelevant to the effect of its low-level dosage EDS product because his study examined the impact of continuous injection of epinephrine into the bloodstream rather than ingestion of pills containing 10 mg or less of EDS.[10] The district court rejected the "mathematical model used [by Dr. Inchiosa] to compare doses of epinephrine to ephedrine." 364 F. Supp. 2d at 1315. To account for the different potency levels of ephinephrine and ephedrine, Dr. Inchiosa factored the greater potency of ephinephrine into his calculations. Dr. Inchiosa's work indicates that he exaggerated margins of error in order to come to a conservative conclusion that the cardiovascular effects produced by a dose of 9 mg of EDS daily may be dangerous.

Further, the FDA did not rely on Dr. Inchiosa's work alone.[11] The FDA's investigation also considered the

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these comments to show that there is absolutely no basis for concluding that [] whole-herb ephedra supplement products present a significant or unreasonable risk. . . ."). The FDA solicited comments on "new scientific evidence . . . concerning health risks associated with the use of dietary supplements containing ephedrine alkaloids." 68 Fed. Reg. 10417 (March 5, 2003). Dr. Inchiosa's study was not among the evidence referenced in the FDA's March notice. *Id.* Given that the FDA did not specifically ask for comments on Dr. Inchiosa's study and Nutraceutical did object to the new scientific evidence generally, it is appropriate for us to consider Nutraceutical's objections to Dr. Inchiosa's study in particular.

[10] Nutraceutical's conclusory allegation that there is insufficient science to support the FDA's conclusion that increased heart rate and blood pressure correlate to increased risk of cardiovascular disease is contrary to the vast scientific evidence in the administrative record.

[11] The FDA relied on multiple studies which demonstrated that EDS raise blood pressure and increase heart rate. The agency considered evidence from the well-known, scientifically established pharmacology of ephedrine alkaloids; peer-reviewed scientific literature on the effects of ephedrine alkaloids; and AERs of occurrences following consumption of EDS. 69 Fed. Reg. 6788. In its call for comments, the

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FDA specifically cited to the following peer-reviewed studies: Stephen Bent, et al., *The Relative Safety of Ephedra Compared with Other Herbal Products,* 138 Ann. Intern. Med. 468-72 (March 2003) (finding that EDS accounted for 64% of all adverse reactions to herbs in the United States, despite representing only 0.82% of herbal product sales); Paul G. Shekelle, et al., U.S. Dep't of Health & Human Servs., Agency for Healthcare Research & Quality, Assessment No. 76, *Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects* (Feb. 2003) (concluding that the use of ephedrine and/or the use of ephedra or ephedrine plus caffeine is associated with two to three times the risk of nausea, vomiting, psychiatric symptoms such as anxiety and change in mood, autonomic hyperactivity, and palpitations); Lewis B. Morgenstern, et al., *Use of Ephedra-Containing Products and Risk for Hemorrhagic Stroke,* 60 J. Neurology 132-35 (2003) (concluding that ephedra is not associated with increased risk for hemorrhagic stroke, expect possibly at higher doses); David Samenuk, et al., *Adverse Cardiovascular Events Temporally Associated With ma huang, an Herbal Source of Ephedrine,* 77 Mayo Clinic Proceedings 12 (2002) (concluding that ephedra use is temporally related to stroke, myocardial infarction, and sudden death; underlying heart or vascular disease is not a prerequisite for ephedra-related adverse events; and the cardiovascular toxic effects associated with ephedra were not limited to massive doses); Christine Haller, et al., *Pharmacology of Ephedra Alkaloids and Caffeine After Single-dose Dietary Supplement Use,* 71 Clinical Pharmacology and Therapeutics 421-32 (June 2002) (after assessing the pharmokinetic effects of a single dose of EDS plus caffeine in eight healthy adults and finding that the mean heart rate response reached a maximum change of 15 beats/minute above the baseline, the authors concluded that dietary supplements that contain ephedra and caffeine can produce significant cardiovascular responses after a single dose); C. Boozer, et. al. *Herbal Ephedra/Caffeine for Weight Loss: a 6-month Randomized Safety and Efficacy Trial,* 26 Int'l J. Obesity Related and Metabolic Disorders 593-604 (2002) (concluding that dietary supplements that contain ephedra and caffeine promote weight and fat loss without the expected decrease in blood pressure); C. Boozer, et al., *An Herbal Supplement Containing Ma Huang-Guarana for Weight Loss: A Randomized, Double-blind Trial,* 25 Int'l J. Obesity and Related Metabolic Disorders, 316-24 (2001) (concluding that dietary supplements that contain ephedra and caffeine promote short-term weight and fat loss, but that safety with long-term use requires further investigation). The FDA also relied on an investigation by the GAO which withdrew its earlier criticism of the FDA's

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findings of the National Institutes of Health, the GAO, and the 1996 Food Advisory Committee, among others. *See also* 364 F. Supp. 2d at 1320-21 ("Dr. Inchiosa . . . states that he cannot determine a safe level of EDS intake. This sentiment is echoed throughout the transcript of the [1996 Food Advisory Committee]. Several of the meeting's attendees made comments that a safe level could not be determined. There was, apparently, not enough evidence to support the conclusion that there is a safe level of intake for EDS."). The review of scientific literature is properly in the province of the FDA, to which this Court grants deference based on its expertise. *See Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 653-54 (1973) (The FDA is "peculiarly suited" to evaluate conflicting scientific reports, a matter "not . . . well left to a court without chemical or medical background," because it "necessarily implicates complex chemical and pharmacological considerations.").

The majority of data in the administrative record suggests that EDS pose an unreasonable threat to the public's health. The FDA:

> looked at the seriousness of the risks and the quality and persuasiveness of the totality of the evidence to support the presence of those risks.

1997 proposed regulation of EDS after linking EDS use with heart attacks, strokes, seizures, death, and cardiac arrest. In addition, Dr. Inchiosa's study discussed the relationship between EDS and epinephrine in a transparent manner. Ephedrine alkaloids are members of a family of pharmacological compounds called sympathomimetics, which mimic the effects of epinephrine in the human body. 69 Fed. Reg. at 6789. Dr. Inchiosa extrapolated data on epinephrine to draw conclusions about EDS, but he did so using peer-reviewed data and generally accepted principles of pharmacology.

> [It] then weighed the risks against the importance of the benefits and the quality and persuasiveness of the totality of the evidence to support the existence of those benefits . . . giv[ing] more weight to benefits that improve health outcomes, especially in the long term, than to benefits that are temporary or rely on subjective measures such as feeling or looking better.

69 Fed. Reg. at 6799. The agency expressed that it would not deem EDS adulterated based on "risks that are insignificant and reasonable in light of the benefits from the supplement. . . ." *Id.* at 6825. The evidence in the administrative record was sufficiently probative to demonstrate by a preponderance of the evidence that EDS at any dose level pose an unreasonable risk. The greater weight of the evidence supports the FDA's ban on EDS, thus satisfying the agency's burden.

The FDA's extensive research identified the dose level at which ephedrine alkaloids present unreasonable risk of illness or injury to be so minuscule that no amount of EDS is reasonably safe. The FDA reasonably concluded that there is no recommended dose of EDS that does not present an unreasonable risk. *Id.* at 6829 ("dose limitations cannot change the unfavorable risk-benefit ratio of [EDS]"). The FDA was not arbitrary or capricious in its Final Rule; the FDA met its statutory burden of justifying a total ban of EDS by a preponderance of the evidence.

We find that the FDA correctly followed the congressional directive to analyze the risks and benefits of EDS in determining that there is no dosage level of EDS acceptable for the market. Summary judgment for plaintiffs was therefore improper, and summary judgment for defendants should have been entered. Accordingly, the district court's

decision is reversed, and we remand for entry of judgment in favor of defendants. As noted above, Nutraceutical's Motion to Correct Oral Argument Record is granted.

REVERSED AND REMANDED.

364 F.Supp.2d 1310

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF UTAH
CENTRAL DIVISION

NUTRACEUTICAL CORPORATION and SOLARAY, INC., Plaintiffs, vs. LESTER CRAWFORD, D.V.M., Acting Commissioner, U.S. Food and Drug Administration, et al., Defendants.	ORDER Case No. 2:04CV409 TC

Plaintiffs Nutraceutical Corp. and Solaray, Inc., ("Plaintiffs") brought this action against Defendants Lester Crawford, D.V.M., Acting Commissioner of the United States Food and Drug Administration, the United States Food and Drug Administration ("FDA"), Tommy Thompson, Secretary of the Department of Health and Human Services, the Department of Health and Human Services, and the United States (collectively "Defendants"), challenging the validity of the FDA's February 2004 regulation banning all ephedrine-alkaloid dietary supplements. Plaintiffs manufacture and sell an ephedrine-alkaloid dietary supplement.

This matter is before the court on Plaintiffs' motion for summary judgment and Defendants' cross-motion for summary judgment. Plaintiffs, bringing this action under the Declaratory Judgment Act, allege that the FDA's Final Rule violates the Food, Drug and Cosmetic Act ("FDCA"), as amended by the Dietary Supplement Health and

Education Act ("DSHEA"), through an improper determination of adulteration under 21 U.S.C. 342(f)[1], and also that it violates the Administrative Procedures Act ("APA").[2]

Plaintiffs seek to have the court: (1) declare the Final Rule invalid; (2) remand the matter to the FDA for further rulemaking consistent with the court's opinion; and (3) enjoin the Defendants from taking enforcement action against Plaintiffs for their sale of a dietary supplement containing 10 mg or less of ephedrine alkaloids per daily dose.

For the reasons set forth below, the court grants the Plaintiffs' motion for summary judgment and denies the Defendants' cross-motion for summary judgment

I. Background

The ephedrine alkaloids used in dietary supplements are naturally occurring stimulant compounds. Ephedrine-alkaloid dietary supplements ("EDS") have been promoted to achieve weight loss, enhance athletic performance and boost energy.

After extensive review, the FDA concluded that all EDS, regardless of the dose suggested in labeling, present an "unreasonable risk of illness or injury." The FDA

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[1] 21 U.S.C. § 342 is the food adulteration provision. Subsection (f) provides the criteria for a determination that a dietary supplement is adulterated. An adulterated food or dietary supplement is not marketable under 21 U.S.C. § 333.

[2] Plaintiffs have voluntarily dismissed their claim of a categorical taking under the Fifth Amendment.

regulation ("Final Rule"), published February 11, 2004, bans the distribution of all such products on the basis that they are adulterated within the meaning of the DSHEA.

Plaintiff Solaray (now owned by Plaintiff Nutraceutical), has manufactured and sold an EDS since 1988. Plaintiffs' product contains 375 mg of *Ephedra sinica* and the labeling recommends one capsule taken no more than twice each day. The recommended dose yields less than 10 mg of ephedrine alkaloids per day. The Final Rule prohibits Plaintiffs from marketing and selling this product.

A. Regulatory Framework

The DSHEA, enacted in 1994 as an amendment to the FDCA, provides that a dietary supplement is adulterated if it presents "a significant or unreasonable risk of illness or injury under" the conditions of use recommended in labeling. 21 U.S.C. § 342(f)(1)(A).

Under the DSHEA, dietary supplements are regulated as a subset of foods unless the supplement producers make disease claims that bring the supplements within the definition of a drug. *See* 21 U.S.C. §§ 321(ff) (defining "dietary supplement"), (g)(1) (defining "drug"); *cf.* 21 U.S.C. § 343(r)(6) (identifies claims which many [sic] be made by manufacturers of dietary supplements and those which are prohibited). Accordingly, dietary supplement manufacturers are not required to provide evidence of product safety and efficacy before marketing their products. Additionally, the DSHEA does not require dietary supplement manufacturers to comply with the post-market product safety monitoring or reporting requirements that the FDCA requires for drugs. The FDA relies on voluntary studies, voluntarily reported adverse event reports

("AERs"), and other data to identify potential safety problems associated with dietary supplements.

B. FDA's Rulemaking

On February 11, 2004, the FDA published the Final Rule declaring EDS adulterated and not legally marketable in the United States. The Final Rule became effective on April 12, 2004.

The Final Rule was the culmination of a long process beginning in the early 1990s when the FDA began receiving AERs reflecting injury and illness associated with the use of EDS. The administrative record reflecting the rulemaking process contains over 133,000 pages of scientific data, expert reviews, comments submitted by interested persons, and other materials considered.

The FDA considered evidence from three principal sources: (1) the well-known, scientifically established pharmacology of ephedrine alkaloids; (2) peer-reviewed scientific literature on the effects of ephedrine alkaloids; and (3) AERS related to the consumption of EDS. 69 Fed.Reg. 6788 (Feb. 11, 2004). The FDA also commissioned expert reviews of the scientific evidence and assessed the findings of the expert reviews. *Id.* at 6802, 6805 & 6814.

1. The 1997 Proposed Rule

The FDA initially published a proposed rule regulating EDS in June of 1997. Under the proposed rule an EDS was adulterated if it contained 8 mg or more of ephedrine alkaloids per serving, or if its labeling suggested or recommended conditions of use that would result in an intake of 8 mg or more during a 6-hour period or a total daily

intake of 24 mg or more of ephedrine alkaloids. 62 Fed.Reg. 30678, 30691 (June 4, 1997). Additionally, the rule proposed to: (1) prohibit EDS labeling for claims or uses requiring long-term intake to achieve the purported effect; (2) prohibit EDS producers from combining ephedrine alkaloids with other stimulant ingredients; (3) require EDS warning statements that would alert consumers to possible drug interactions, and directing consumers not to take the product for more than seven days; (4) require EDS warning statements providing further advice for at-risk consumers; and (5) require that claims encouraging short-term excessive intake be accompanied with a statement that warned that the recommended intake may result in serious adverse health effects. *Id.* at 30691-704.

Upon receiving a request from the House Committee on Science, the Government Accounting Office ("GAO") released a report entitled "Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids." 65 Fed.Reg. 17474 (Apr. 3, 2000). In this report the GAO recommended that the FDA "provide stronger evidence on the relationship between the intake of [EDS] and the occurrence of adverse reactions that support the proposed dosing level and duration of use limits." *Id.* at 17475. Further, the GAO noted that the FDA "should consider additional information . . . to determine whether a dietary ingredient limit, or some alternative approach, would be appropriate to regulate [EDS]." 65 Fed.Reg. at 17475.

In light of the GAO's conclusions and other comments, on April 3, 2000, the FDA partially withdrew the proposed rule. Specifically, the FDA withdrew the restrictions on dosages and directions for frequency of use and the proposed prohibition on labeling claims for uses encouraging

long-term intake. The FDA also withdrew the proposed warnings advising consumers not to exceed the recommended dosages or use the product for more than seven days. The FDA retained the other warning statements and the proposed prohibition on combining EDS with other stimulant ingredients. *Id.* at 17475-76.

After this partial withdrawal of the proposed rule, the FDA reopened the comment period three times and considered additional evidence.

2. The 2004 Final Rule

The notice reopening the comment period on March 5, 2003, stated that the FDA intended to consider whether the "FDA should determine that [EDS] present a 'significant or unreasonable risk of illness or injury'" and sought comments on that issue. 68 Fed.Reg. 10417, 10419 (March 5, 2003) (quoting 21 U.S.C. § 342(f)(1)(A)).

The FDA published the Final Rule on February 11, 2004. The FDA concluded that when the minimal benefits of EDS are weighed against the substantial risks, all EDS present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or if no conditions or use are suggested or recommended in labeling, under ordinary conditions of use. 69 Fed.Reg. at 6788. Because it found that use of EDS does not provide a benefit sufficient to outweigh the increased risk of heart attack, stroke, and death, the FDA concluded that all EDS pose an unreasonable risk and are adulterated under the DSHEA. *Id.* at 6789.

C. FDA's Statutory Interpretation and the Final Rule

The FDA promulgated the Final Rule under the DSHEA, which provides:

> A food shall be deemed to be adulterated –
>
> * * *
>
> (f) Dietary supplement or ingredient: safety
>
> (1) If it is a dietary supplement or contains a dietary ingredient that–
>
> (A) presents a significant or unreasonable risk of illness or injury under –
>
> (i) conditions of use recommended or suggested in labeling, or
>
> (ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use;
>
> . . .
>
> In any proceeding under this subparagraph, the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated. The court shall decide any issue under this paragraph on a de novo basis.

21 U.S.C. § 342(f)(1).

The summary of the Final Rule closely follows the language of the statute:

> The [FDA] is issuing a final regulation declaring dietary supplements containing ephedrine alkaloids adulterated under the [FDCA] because they present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in labeling, under ordinary conditions of use.

69 Fed.Reg. at 6788.

The FDA concluded that the words "significant" and "unreasonable" have two separate and independent meanings. Under the FDA's statutory construction, "significant" involves an evaluation of risk alone, while "unreasonable" requires a comparison of risks and benefits. *Id.* at 6823 ("A risk could be significant, but reasonable if the benefits were great enough to outweigh the risks."). The Final Rule does not include a consideration of the word "significant." The record indicates that the FDA believed that evaluation of EDS under the "significant" standard was unnecessary because it is included within the statute as an alternative to "unreasonable." *Id.* at 6788 & 6822-23 (*see also* Def. Mem. Supp. Cross-Mot. Summ. J. at 31 n.14 ("Because the FDA concluded that EDS pose an unreasonable risk, it was not necessary for the agency to address DSHEA's significant risk standard.")).

D. The FDA's Findings

EDS have been promoted to help achieve weight loss, enhance athletic performance, increase energy levels, ease breathing, and for other similar uses. The FDA determined that these effects are temporary, of modest benefit, and do not improve health if they occur at all. 69 Fed.Reg. at 6822 & 6826. The FDA found that although there is

evidence to support modest, short-term weight loss, the FDA could not determine whether that weight loss results in improved health outcomes. Specifically, the FDA could not determine whether EDS have a positive effect on cardiovascular risk factors associated with being overweight. *Id.* at 6789, 6818-21, 6825-26.

The FDA found that EDS, generally, increase the risk of serious adverse events, including heart attacks, stroke, and death. *Id.* at 6789, 6800-04. An evaluation of single-dose studies showed that EDS cause an increase in heart rate and blood pressure in healthy subjects. A multiple-dose study demonstrated a higher blood-pressure measurement after one month of continued exposure to a combination of EDS and caffeine. *Id.* at 6801-02. The FDA also reviewed studies observing increased mortality in people with congestive heart failure who were treated with substances similar to EDS. *Id.* Additional evidence of the negative effects of EDS was obtained through 3,000 AERs submitted directly to the FDA and 16,000 reports from records maintained by Metabolife, one of the largest distributors of EDS.

Plaintiffs' product is labeled with a recommended daily dose of approximately 10 mg of ephedrine alkaloids. Therefore, the key evidence is that which the FDA contends shows a significant or unreasonable risk of illness or injury at recommended dosages of 10 mg per day or less. The FDA points the court to 69 Fed.Reg. 6788, References 84-87 ("Reference") as the relevant sections.

References 84 and 85 are a series of letters between the FDA and Dr. Mario A. Inchiosa written between May and July of 1999. The letters are a response by Dr. Inchiosa to a request from the FDA that he conduct a scientific

review on the effects of ephedrine alkaloids. The letters contain Dr. Inchiosa's conclusions derived from the examination of various studies of intake of substances *similar* to ephedrine. Dr. Inchiosa performed a pharmacokinetic analysis[3] comparing epinephrine to ephedrine. According to Dr. Inchiosa, epinephrine and ephedrine alkaloids produce similar effects in the human body, but at different potencies.[4] He also used studies of the effects of injections of epinephrine to derive conclusions about the effects of ephedrine alkaloids. Acceptance of Dr. Inchiosa's conclusions depends on the acceptance of a mathematical model used to compare doses of epinephrine to ephedrine.

Dr. Inchiosa specifically refers to a study performed by W.E. Clutter, et al., ("Clutter Study"), in which the administration of epinephrine increased heart rate and blood pressure. *See* W.E. Clutter, et al., *Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolis and hemodynamic actions in man,* 1980 J. Clin. Invest. 66, 94-101 (cited in Reference 84 at 4 & 6). Dr. Inchiosa's mathematical model demonstrates that a "chronic ephedrine dose of 1.5 mg every four hours" would produce the same effects as epinephrine did in the Clutter Study. Reference 84 at 4. Dr. Inchiosa concluded that: "In the absence of a clinical indication, it would not be possible to recommend a safe dose of ephedra." *Id.* Other than the conclusions about ephedrine drawn from the Clutter Study

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[3] A pharmacokinetic analysis is one which examines the bodily absorption, distribution, metabolism, and excretion of drugs. *Webster's New Collegiate Dictionary* 852 (G. & C. Merriam 1979).

[4] In Reference 84, Dr. Inchiosa indicates that various studies have shown that epinephrine is between 41 and 69 times more potent than ephedrine. These potency ratios serve as the basis of his analysis. Reference 84 at 4-5.

on the effects of epinephrine, there is no evidence in the administrative record pertaining specifically to doses of ephedrine at the ephedrine-alkaloid levels recommended by Plaintiffs, that is, 10 mg per day.

References 86 and 87 are excerpts from the transcript of the FDA's Food Advisory Committee on Dietary Supplements Containing Ephedrine Alkaloids Meeting held on August 26-27, 1996. The transcript demonstrates that several physicians and researchers were unable to conclude that there is a safe dosage level for EDS. For example, Dr. Georgitis stated, "I obviously cannot identify [a safe level]. There's no scientific data which shows that 1 milligram is any better than 5, which is any better than 10, which is any better than 30, and that goes both for the ephedrine alkaloid and for ephedrine itself." Reference 86 at 136. Dr. Ricaurte noted that part of the difficulty in identifying a safe level of EDS is that "[t]here is uncertainty . . . [in] the available data with regard to the ephedrine alkaloids themselves[.]" *Id.* at 221. Dr. Marangell expressed concern regarding "the serious adverse events in the 1- to 5-milligram range. . . . [W]e don't have a lot of data on that, and perhaps for many people that's fine, but . . . individual variation is going to play as much of a role as a particular dose level is." *Id.* at 229. Reference 87 duplicates much of what is discussed in Reference 86.

In sum, those present at the meeting concluded that it is difficult or impossible to identify any safe recommended dosage level for EDS.

II. Analysis

The parties' motions ask the court to determine whether the Final Rule banning all EDS violates 21 U.S.C.

§ 342(f). To resolve this issue the court must answer: first, whether the FDA's use of a risk-benefit analysis is appropriate under the DSHEA; and second, whether the FDA has provided sufficient evidence to support the conclusion that EDS containing 10 mg or less per day of ephedrine alkaloids pose a significant or unreasonable risk of illness of injury.[5]

A. Scope of Review

While styled as cross-motions for summary judgment, this is actually an appeal from the decision of an administrative agency. Accordingly, the court must apply the standards for an appeal. *See Olenhouse v. Commodity Credit Corp.*, 42 F.3d 1560, 1580 (10th Cir. 1994); *Southern Utah Wilderness Alliance v. B.L.M.*, 147 F.Supp.2d 1130, 1135-36 (D.Utah 2001). In a review of an administrative decision under the APA, the parties are typically not permitted to supplement the evidence in the administrative record. *See e.g., Roberts v. Morton,* 549 F.2d 158, 160 (10th Cir. 1976) ("Such review is confined to the agency record or such portions of it which the parties may cite, and additional evidence is not to be admitted.") (citing *Nickol v. United States,* 501 F.2d 1389, 1390 (10th Cir. 1974)).

[5] Because of the court's answers to these two questions, it need not determine whether the FDA properly omitted the term "significant" from its construction of the statute or whether it complied with the notice and comment procedures of the APA.

B. Deference

The final sentence of 21 U.S.C. § 342(f) provides that: "The court shall decide any issue under this paragraph on a de novo basis." The parties agree that this provision requires the court to examine all factual determinations on a de novo basis. The parties do not agree, however, on whether the court should review the FDA's statutory construction de novo or whether the court should accord the FDA's conclusions deference under *Chevron USA, Inc. v. Nat. Res. Def. Council, Inc.*, 467 U.S. 837 (1984). The court, reviewing the Final Rule under *Chevron*, need not reach the question of whether the FDA's statutory construction should be reviewed de novo.

Under *Chevron*, a court must first determine whether Congress has spoken to the precise question at issue. *Chevron*, 467 U.S. at 842; *see also FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000); *Pharmanex v. Shalala*, 221 F.3d 1151, 1154 (10th Cir. 2000). If Congress' intent is clear and unambiguous, the analysis is complete and Congress' intent controls. "In a statutory construction case, the beginning point must be the language of the statute, and where the statute speaks with clarity to an issue[,] judicial inquiry into the statute's meaning . . . is finished." *Estate of Cowart v. Nicklos Drilling Co.*, 505 U.S. 469, 475 (1992).

"As a general rule of statutory construction, a statute is ambiguous if it is 'capable of being understood in two or more possible senses or ways.'" *Houghton ex. rel. Houghton v. Reinertson*, 382 F.3d 1162, 1169 (10th Cir. 2004) (quoting *Chickasaw Nation v. United States*, 534 U.S. 84, 90 (2001)); *see also, Allen v. Geneva Steel Co.*, 281 F.3d 1173, 1178 (10th Cir. 2002) ("[A]mbiguity exists when a

statute is capable of being understood by reasonably well-informed persons in two or more different senses.") (quotation omitted). The ambiguity of a statute is determined "by reference to the language itself, the specific context in which the language is used, and the broader context of the statute as a whole." *Houghton,* 382 F.3d at 1169 (citing *Robinson v. Shell Oil Co.,* 519 U.S. 337, 341 (1997)).

If a court finds that the statute is silent or ambiguous as to the specific issue, the question is whether the agency's answer is "based on a permissible construction of the statute." *Chevron,* 467 U.S. at 842-43. Under *Chevron,* a court must accord deference to an administrative agency's reasonable interpretation of a statute. *Chevron,* 467 U.S. at 843-44 & n. 11; *see also United States v. Mead Corp.,* 533 U.S. 218, 229 (2001) ("reviewing court has no business rejecting an agency's exercise of its generally conferred authority to resolve a particular statutory ambiguity simply because the agency's resolution seems unwise") (citations omitted). A court must "give effect to the agency's interpretation unless it is arbitrary, capricious, or manifestly contrary to the statute." *Pharmanex,* 221 F.3d at 1154. The decision as to what a statute means, however, is "the quintessential judicial function." *BATF v. FLRA,* 464 U.S. 89, 98 (1983). The question of statutory interpretation ultimately rests with the court. *Chevron,* 467 U.S. at 843 n.9.

With these principles in mind, the court turns to the questions at issue.

C. Was the FDA's use of a risk-benefit analysis appropriate under the DSHEA?

In promulgating the Final Rule, the FDA relied upon a risk-benefit test to determine whether the risk presented by EDS is unreasonable and argues that this is a proper construction of the statute. 69 Fed.Reg. at 6788. Plaintiffs have asserted that the application of this test is an improper interpretation of the statute because it adds language not intended by Congress and has the effect of shifting the burden of proof from the government to the manufacturers of EDS contrary to Congress' intent to harmonize the treatment of dietary supplements with that of food generally. The plain language of the DSHEA does not require a comparison of benefits and risks.

The pertinent portion of 21 U.S.C. § 342(f) states that a dietary supplement shall be deemed adulterated if it "presents a significant or unreasonable risk of illness or injury." 21 U.S.C. § 342(f)(1)(A). The FDA contends that the plain meaning of the term "unreasonable" in the statute requires a risk-benefit analysis: "In the absence of a sufficient benefit, the presence of even a relatively small risk of an important adverse health effect to a user may be unreasonable." 69 Fed.Reg. at 6788. The FDA argues that this construction is consistent with Congress' definition of the term "unreasonable risk" in other parts of the same statute and other portions of similar statutes. Specifically, the FDA refers the court to the provisions of the FDCA governing medical devices and also the Toxic Substances Control Act ("TSCA"). *See* 21 U.S.C. § 360c(a)(1); H. Rep. 94-853, 94th Cong. 2d Sess. 19 (1976) ("the requirement that risk be unreasonable contemplates a balancing of the possibility that illness or injury will occur against the benefits of use."); 15 U.S.C. § 2605(a); H. Rep. 94-1341,

94th Cong., 2d Sess. 14 (1976) (defining "unreasonable risk" in the context of the TSCA as "balancing the probabilities that harm will occur and the magnitude and severity of that harm against the effect of proposed regulatory action on the availability to society of the benefits of the substance or mixture").

Defendants' reliance on the medical device provisions of the FDCA to justify the inclusion of a risk-benefit test for dietary supplements is misplaced. The provision governing the safety and effectiveness of medical devices specifically calls for a risk-benefit analysis:

> For purposes of this section and sections 360d and 360e of this title, the safety and effectiveness of a device are to be determined –
>
> . . .
>
> (C) *weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.*

21 U.S.C. § 360c(a)(2) (emphasis added). The DSHEA contains no such provision. Unlike medical devices and drugs, dietary supplements are not classified on the basis of a risk-benefit analysis. *Cf.* 21 U.S.C. §§ 355(b) (requiring that an application for a new drug show that it is effective for its intended use); 360c(a)(1)(A), (B) & (C) (all three classes of medical devices have effectiveness requirements).

The FDCA, in defining dietary supplements, states: "Except for the purposes of section 201(g), a dietary supplement shall be deemed a food within the meaning of this Act." 21 U.S.C. § 321(ff). A brief look at the legislative history of the DSHEA indicates that Congress generally

intended to harmonize the treatment of dietary supplements with that of foods when it added the dietary supplement subsection to the food adulteration provision. Sen. Rep. No. 103-410 at 21 ("Section 402 [of the FDCA] is the provision that establishes the grounds upon which the [FDA] may deem a food (including a dietary ingredient) to be adulterated"). "Under present law, a dietary supplement, *as with any food, is presumed to be safe.*" *Id.* at 22 (emphasis added). Food producers are not required to establish a benefit before sale.[6]

The FDA's imposition of a risk-benefit analysis places a burden on the producers of EDS to demonstrate a benefit as a precondition to sale, and that is contrary to Congress' intent. Congress unequivocally stated that "[i]n any proceeding under this subparagraph, the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated." 21 U.S.C. § 342(f). Proof of adulteration is the sole responsibility of the FDA: "[A dietary supplement, as with any food,] may be lawfully marketed, unless and until the FDA, by a preponderance of the evidence, shows that the supplement is 'injurious to health.'" Sen. Rep. No. 103-410 at 21. The imposition of a risk-benefit analysis requires the producer of an EDS to establish a benefit and alleviates the burden Congress placed squarely on the government to demonstrate the existence of a significant or unreasonable risk.

For the above reasons, the court concludes that the FDA's requirement that EDS demonstrate a benefit is

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[6] As pointed out by Plaintiffs, if food producers were required to show a benefit as a precondition to sale, the sale of foods such as potato chips might be prohibited.

contrary to the clear intent of Congress. For those same reasons, the FDA's definition of "unreasonable" entailing a risk-benefit analysis is also improper.

D. Has the FDA provided evidence to support the conclusion that EDS containing 10 mg or less per day of ephedrine alkaloids pose a significant or unreasonable risk of illness of [sic] injury?

Under 21 U.S.C. § 342(f), "the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated." The government must establish that EDS pose a significant or unreasonable risk by a preponderance of the evidence. *See* Sen. Rep. No. 103-410 at 36 ("By the last sentence of [§ 342(f)], it is intended to codify current law that the government bear the burden of proving dietary supplements adulterated. The government must produce the preponderance of the evidence as to the harmful effects from the dietary supplement when used as recommended and suggested in the labeling.") (citing *United States v. 71/55 Gallon Drums of Stuffed Green Olives,* 790 F.Supp. 1379 (N.D.Ill.1992)).[7]

[7] The courts have long required the FDA to prove adulteration by a preponderance of the evidence. *See United States v. 5 Cases More of Less Containing "Figlia Mia Brand"*, 179 F.2d 519, 524 (2d Cir.1950) ("This is a civil proceeding in which the usual rule as to burden of proof [preponderance of the evidence] prevails."); *71/55 Gallon Drums of Stuffed Green Olives,* 790 F.Supp. at 1382 ("The burden of proof rests on the government to establish by a 'fair preponderance of the evidence' that the article of food is adulterated within the meaning of § 342(a)(3)." (citation omitted)); *see also United States v. 233 Tins of Strawberries,* 175 F.Supp. 694, 699 (D.Ark.1959); *United States v. Anderson Seafoods, Inc.*, 447 F.Supp. 1151 (N.D.Fla.1978) ("A preponderance of the evidence shows that some unquantified portion of the mercury in swordfish is attributable to the acts of man.").

The statute reads that the government's burden is met only if it has demonstrated the presence of a risk "under conditions of use recommended or suggested in labeling." 21 U.S.C. § 342(f)(1)(A)(i). The plain language of the statute requires a dose-specific analysis. Legislative history also confirms Congress' intent to require that a finding of adulteration be dose-specific: "a safety finding cannot be entered against a supplement based upon a dosage not recommended to consumers in the labeling." Sen. Rep. No. 103-410 at 36.

Simply stated, to declare all EDS adulterated, as it has done, the FDA must prove that any dose amount, no matter how small, presents a significant or unreasonable risk of illness or injury. Specifically, because the Plaintiffs' suggested dosage recommends no more than 10 mg of ephedrine alkaloids per day, the proper focus here is on the evidence the FDA presented regarding the risks of low-dose EDS. To this end, the Defendants have directed the court specifically to 69 Fed.Reg. 6788, References 84, 85, 86, and 87.

Reference 84, the Inchiosa review, concludes that "a chronic ephedrine dose of 1.5 mg every 4 hours" (a daily dose of 9 mg) would cause "increases in heart rate and systolic blood pressure." Reference 84 at 4. This conclusion, contained in one six-page letter to the FDA, is the only specific reference in the administrative record to the effects of low-dose EDS. The Inchiosa review derives the potential physiological effects of orally ingested ephedrine from data obtained regarding intravenous injections of epinephrine. He used a hypothetical mathematical model to perform a pharmacokinetic analysis of the effects of

ephedrine alkaloids. There is no specific data involving the oral ingestion of 10 mg per day of EDS.[8]

Dr. Inchiosa's conclusions rest on a comparison of potency rates between epinephrine and ephedrine alkaloids. Dr. Inchiosa reviewed studies indicating that epinephrine is between 41 and 69 times more potent than ephedrine. *Id.* at 1-2. The data and its application to ephedrine alkaloids are applicable only upon acceptance of Dr. Inchiosa's mathematical model. In Reference 85, however, Dr. Inchiosa also states that the onset of the effects of ephedrine alkaloids would vary depending on the source of the alkaloids and the actual rates of absorption which weakens his general conclusions regarding the intake of low-dose EDS. Reference 85 at 1-2. Dr. Inchiosa's conclusion that 9 mg per day of ephedrine alkaloids produces negative health effects is based upon *chronic* intake, which is not the condition of use suggested on the labeling of Plaintiffs' product. This evidence cannot, on its own, support a conclusion that a recommended dose of 10 mg per day of EDS presents a significant or unreasonable risk.

Dr. Inchiosa also states that he cannot determine a safe level of EDS intake. This sentiment is echoed throughout the transcript of the FDA's Food Advisory Committee on Dietary Supplements Containing Ephedrine Alkaloids Meeting held on August 26-27, 1996 (References

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[8] The only dose-specific data provided by Dr. Inchiosa pertaining to low-dose EDS is that the harmful effects of ephedrine would be felt with a "chronic ephedrine dose of 1.5 mg every four hours." Reference 84 at 4. This data was derived not from a study involving the oral ingestion of ephedrine alkaloids, but from a derivative analysis relying on Dr. Inchiosa's mathematical model.

86 and 87). Several of the meeting's attendees made comments that a safe level could not be determined. There was, apparently, not enough evidence to support the conclusion that there is a safe level of intake for EDS.

A negative inference is different from the affirmative proof required by 21 U.S.C. § 342(f). The statute requires an affirmative demonstration of "significant or unreasonable" risk at a particular dose level to support a finding of adulteration. There is not sufficient evidence in the administrative record to establish that the risks identified by the FDA are associated with the intake of low-dose EDS. The statement that a safe level cannot be determined is simply not sufficient to meet the government's burden. To find otherwise would be to place the burden on the manufacturers of EDS to show that their recommended dosages *are* safe. This would be directly contrary to the statutory language placing the burden of proof on the government and to the intent of Congress in regulating dietary supplements as food.

The FDA, by failing to prove by a preponderance of the evidence that a dosage of 10 mg or less of ephedrine alkaloids presents a significant or unreasonable risk of illness or injury, has failed to give effect to the dose-specific language of 21 U.S.C. § 342(f)(1)(A)(i).

ORDER

Accordingly, Plaintiffs' motion for summary judgment (Dkt. 7) is GRANTED and Defendants' cross-motion for summary judgment (Dkt. 14) is DENIED.

The court remands to the FDA for further rulemaking consistent with this Order and enjoins Defendants from

taking enforcement action against Plaintiffs for their sale of a dietary supplement containing 10 mg or less of ephedrine alkaloids per daily dose.

SO ORDERED this 13 day of April, 2005.

BY THE COURT:

/s/ Tena Campbell
TENA CAMPBELL
United States District Judge

UNITED STATES COURT OF APPEALS

FOR THE TENTH CIRCUIT

NUTRACEUTICAL CORPORATION; SOLARAY, INC., Plaintiffs-Appellees, v. ANDREW VON ESCHENBACH, Acting Commissioner, U.S. Food and Drug Administration; UNITED STATES FOOD AND DRUG ADMINISTRATION; MICHAEL O. LEAVITT, Secretary of the Department of Health and Human Services; DEPARTMENT OF HEALTH AND HUMAN SERVICES; UNITED STATES OF AMERICA, Defendants-Appellants.	No. 05-4151

ORDER

Filed October 16, 2006

Before **KELLY, TYMKOVICH**, Circuit Judges and **EAGAN**,* District Judge.

Appellees' petition for rehearing is denied.

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* The Honorable Claire V. Eagan, District Judge, United States District Court for the Northern District of Oklahoma, sitting by designation.

The petition for rehearing en banc was transmitted to all of the judges of the court who are in regular active service. As no member of the panel and no judge in regular active service on the court requested that the court be polled, that petition is also denied.

Entered for the Court
ELISABETH A. SHUMAKER, Clerk

by: /s/ _____
Deputy Clerk

69 Fed. Reg. 6788 (Feb. 11, 2004)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 119

[Docket No. 1995N-0304]

RIN 0910-AA59

Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA, we, our) is issuing a final regulation declaring dietary supplements containing ephedrine alkaloids adulterated under the Federal Food, Drug, and Cosmetic Act (the act) because they present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in labeling, under ordinary conditions of use. We are taking this action based upon the well-known pharmacology of ephedrine alkaloids, the peer-reviewed scientific literature on the effects of ephedrine alkaloids, and the adverse events reported to have occurred in individuals following consumption of dietary supplements containing ephedrine alkaloids.

DATES: This rule is effective on April 12, 2004.

FOR FURTHER INFORMATION CONTACT: Wayne Amchin, Center for Food Safety and Applied Nutrition (HFS-007), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-6733.

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I. Introduction

A. Why Have We Concluded That Dietary Supplements Containing Ephedrine Alkaloids Present an Unreasonable Risk?

We conclude that dietary supplements containing ephedrine alkaloids are adulterated under section 402(f)(1)(A) (21 U.S.C. 342(f)(1)(A)) of the act because they present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in labeling, under ordinary conditions of use. Dietary supplements containing ephedrine alkaloids are most often used for weight loss, energy, or to enhance athletic performance.

By its plain language, section 402(f)(1)(A) of the act requires evidence of "significant or unreasonable risk" of illness or injury. There is no requirement that there be evidence proving that the product has caused actual harm to specific individuals, only that scientific evidence supports the existence of risk. The Government's burden of proof for "unreasonable risk" is met when a product's risks outweigh its benefits in light of the claims and directions for use in the product's labeling or, if the labeling is silent, under ordinary conditions of use. "Unreasonable risk," thus, represents a relative weighing of the product's known and reasonably likely risks against its known and reasonably likely benefits. In the absence of a sufficient benefit, the presence of even a relatively small risk of an important adverse health effect to a user may be unreasonable. Because it is not reasonable to conclude that a product is too risky in the absence of any significant evidence, some weight of evidence of risk is required to meet this standard. For example, isolated adverse events alone might not be expected to constitute substantiation of risk, but adverse event reports combined with pharmacological and other clinical evidence might be expected to do so.

In considering whether dietary supplements containing ephedrine alkaloids present an unreasonable risk, we considered evidence from three principal sources: (1) The well-known, scientifically established pharmacology of ephedrine alkaloids; (2) peer-reviewed scientific literature on the effects of ephedrine alkaloids; and (3) the adverse events (including published case reports) reported to have occurred following consumption of dietary supplements containing ephedrine alkaloids.

Ephedrine alkaloids are members of a large family of pharmacological compounds called sympathomimetics. Sympathomimetics mimic the effects of epinephrine and norepinephrine, which occur naturally in the human body. Multiple studies demonstrate that dietary supplements containing ephedrine alkaloids, like other sympathomimetics, raise blood pressure and increase heart rate. These products expose users to several risks, including the consequences of increased blood pressure (*e.g.*, serious adverse events such as stroke, heart attack, and death) and increased morbidity and mortality from worsened heart failure and pro-arrhythmic effects. Based on the best available scientific data and the known pharmacology of ephedrine alkaloids and similar compounds, we conclude that dietary supplements containing ephedrine alkaloids pose short-term and long-term risks. This is clearest in long-term use, where sustained increased blood pressure in any population will increase the risk of stroke, heart attack, and death, but there is also evidence of risk from shorter-term use in patients with heart failure or underlying coronary artery disease.

The data do not indicate that these products provide a health benefit sufficient to outweigh these risks. The best clinical evidence for a benefit is for weight loss, but even there the evidence supports only a modest short-term weight loss, insufficient to positively affect cardiovascular risk factors or health conditions associated with being overweight or obese. Even if long-term weight loss could be achieved with the use of dietary supplements containing ephedrine alkaloids, we believe that the risks posed by these products when used continuously in the long term generally could not be adequately mitigated except through physician supervision. Other possible benefits,

such as enhanced athletic performance, enhanced energy, or a feeling of alertness, lack scientific support and/or provide only temporary benefits that we consider trivial compared to the risks of these products, which may include long-term or permanent consequences like heart attack, stroke, and death. Therefore, we have determined that the risks of dietary supplements containing ephedrine alkaloids, when used for their labeled indications or under ordinary conditions of use, outweigh the benefits of these products. We do not believe these risks can be adequately mitigated through other regulatory measures available to FDA for dietary supplements, such as warnings in labeling.

As with other sympathomimetics, we believe that the risks posed by dietary supplements containing ephedrine alkaloids, when used continuously over the long term, generally cannot be adequately mitigated except through physician supervision. Similar to over-the-counter (OTC) single ingredient ephedrine and pseudoephedrine products, we expect that dietary supplements containing ephedrine alkaloids could be marketed without physician supervision for a very temporary, episodic use that provides a benefit that outweighs the known and reasonably likely risks of these products. However, we are currently unaware of any such use, and our experience with ephedrine alkaloid-containing OTC drug products suggests that such benefits will be demonstrable only for disease uses.

B. What Are the Ephedrine Alkaloids and Where Do They Come From?

The ephedrine alkaloids, including, among others, ephedrine, pseudoephedrine, norephedrine, methylephedrine, norpseudoephedrine, methylpseudoephedrine, are

chemical stimulants that occur naturally in some botanicals (Refs. 1 through 5), but can be synthetically derived. The ingredient sources of the ephedrine alkaloids in dietary supplements include raw botanicals (i.e., plants) and extracts from botanicals. Ma huang, *Ephedra*, Chinese *Ephedra*, and epitonin are several names used for botanical ingredients, primarily from *Ephedra sinica* Stapf, *Ephedra equisetina* Bunge, *Ephedra intermedia* var. tibetica Stapf and *Ephedra distachya* L. (the *Ephedras*), that are sources of ephedrine alkaloids (Refs. 1, 6, and 7). Other plant sources that contain ephedrine alkaloids include *Sida cordifolia* L. and *Pinellia ternata* (Thunb.) Makino (Refs. 8 and 9). Common names that have been used for the various plants that contain ephedrine alkaloids include sea grape, yellow horse, joint fir, popotillo, and country mallow. The names desert herb, squaw tea, Brigham tea, and Mormon tea refer to North American species of *Ephedra* that do not contain ephedrine alkaloids but have been misused to identify ephedrine alkaloid containing ingredients. Although the proportions of the various ephedrine alkaloids in botanical species vary from one species to another, in most species used commercially, ephedrine is typically the predominant alkaloid in the raw material (Ref. 10).

Dietary supplements containing ephedrine alkaloids are widely sold in the United States (Refs. 11 through 13).[1]

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[1] We use the term "dietary supplements containing ephedrine alkaloids" in this final rule to refer to dietary supplements containing botanical sources of ephedrine alkaloids. We use the term "ephedra" to refer to botanical sources of ephedrine alkaloids, whether derived from a member of the *Ephedra* genus or another botanical, such as *Sida cordifolia* L. or *Pinellia ternata* (Thunb.) Makino. We use the term "*Ephedra*" to refer specifically to the Ephedra genus of plants.

Over the last decade, dietary supplements containing ephedrine alkaloids have been labeled and used primarily for weight loss, energy, or to enhance athletic performance. Additional scientific evidence, and numerous reports of serious adverse events, including death, following consumption of dietary supplements containing ephedrine alkaloids, have raised concerns about their safety. Consequently, we have taken a number of actions in an attempt to protect the public from the risks of these products.

C. What Regulatory Actions Have We Taken Regarding Dietary Supplements Containing Ephedrine Alkaloids?

In the **Federal Register** of June 4, 1997 (62 FR 30678) (June 1997 proposal), we published a proposed rule on dietary supplements containing ephedrine alkaloids. In this document, we proposed to make a finding, with the force and effect of law, that a dietary supplement is adulterated if it contains 8 milligrams (mg) or more of ephedrine alkaloids per serving, or if its labeling suggests or recommends conditions of use that would result in an intake of 8 mg or more in a 6-hour period or a total daily intake of 24 mg or more of ephedrine alkaloids. The June 1997 proposal would also have required that the label of dietary supplements containing ephedrine alkaloids state that the product should not be used for more than 7 days. We also proposed to prohibit the use of ephedrine alkaloids in dietary supplements with other ingredients that have a known stimulant effect that may interact with ephedrine alkaloids, and to prohibit labeling claims, such as weight loss or body building, that require long-term intake to achieve the purported effect. In addition, the June 1997 proposal would have required a statement accompanying

claims that encourage short-term excessive intake to enhance a purported effect, such as an increase in energy, that taking more than the recommended serving may result in serious adverse health effects. We also proposed to require that the labels of all dietary supplements containing ephedrine alkaloids bear a statement warning consumers not to use the product if they are taking certain drugs; advising them to contact a health care professional before use if they have certain diseases or health conditions; and warning them to stop use and call a health care professional if they develop certain signs or symptoms. We proposed these actions in response to reports of serious illnesses and injuries, including a number of deaths, associated with the use of dietary supplements containing ephedrine alkaloids and our investigations and assessment of these illnesses and injuries. These actions were also supported by many of the recommendations made during the October 1995 meeting of an ad hoc Working Group of the FDA Advisory Committee (Working Group) and the August 1996 meeting of the Food Advisory Committee (FAC) and the Working Group concerning the potential public health problems associated with the use of dietary supplements containing ephedrine alkaloids and what action FDA should take to address the serious health concerns associated with their use (Refs. 14 and 15).

The comment period for the June 4, 1997, proposed rule ended on August 18, 1997. In a document published in the **Federal Register** of August 20, 1997 (62 FR 44247), we announced our intent to reopen the comment period after we corrected a number of inadvertent omissions in the administrative record. Subsequently on September 18, 1997 (62 FR 48968), we reopened the comment period until December 2, 1997.

During this second comment period, the Commission on Dietary Supplement Labels (the Commission) released its final report on November 24, 1997. The Commission, an independent agency established by section 12 of the Dietary Supplement Health and Education Act of 1994 (DSHEA) (Public Law 103-417), was charged with conducting a study on, and providing recommendations for, the regulation of label claims and statements for dietary supplements. The Commission's members included several scientists from academia and industry. In its report, the Commission divided its conclusions into three categories: findings, guidance, and recommendations. The Commission Report defined "findings" as conclusions reached by the Commission based on information and data it received during its deliberations. The Commission defined "guidance" that was directed to FDA as advice that we should consider as we developed or implemented activities related to the availability of dietary supplements in the marketplace. The Commission defined "recommendations" as suggested changes to FDA regulations or the development of new regulations governing dietary supplements.

One guidance statement in the Commission Report pertains to the safety of dietary supplements containing ephedrine alkaloids. In the report, the Commission urges FDA to use its authority under DSHEA to take swift enforcement action to address potential safety issues such as those posed recently by products containing ephedrine alkaloids. While it is expected that a responsible industry will avoid marketing unsafe products and that the industry will react promptly to remove products shown to be associated with significant or serious adverse events, in the final analysis there must be a strong and reliable enforcement system to back up the safety provisions of

DSHEA. Failure by FDA to act when strong enforcement is needed undermines public confidence in the ability of not only the Federal Government but also the dietary supplement industry to ensure safety and avoid harm to the public (Ref. 16 at p. VII of Executive Summary).

In a notice published in the **Federal Register** on April 29, 1998 (63 FR 23633), we announced our views on the recommendations and guidance of the Commission, as presented in the Commission's report. In this notice, we stated that we take seriously our public health protection mission and are committed to removing unsafe dietary supplements from the market (63 FR 23633 at 23634). The direction taken in the current rulemaking on dietary supplements containing ephedrine alkaloids is consistent with the Commission's advice.

In September 1998, the U.S. General Accounting Office (GAO) began a study on FDA's June 1997 proposal. GAO's work culminated in the issuance of a July 1999 report (Ref. 17). GAO concluded that the evidence supported concern that ephedrine alkaloid-containing supplements can cause serious health problems and it recommended further data collection and review. At the same time, GAO criticized FDA's reliance on adverse event reports (AERs) as the basis for the proposed restrictions on dosage, frequency and duration of use.

In the **Federal Register** of April 3, 2000 (65 FR 17474, April 3, 2000), we withdrew parts of the June 1997 proposal. More specifically, we withdrew the proposed finding that a dietary supplement is adulterated if it contains 8 mg or more of ephedrine alkaloids per serving, or if its labeling suggests or recommends conditions of use that would result in the intake of 8 mg or more in a 6-hour

period or a total daily intake of 24 mg or more of ephedrine alkaloids; the proposed compliance procedures (regarding the analytical method FDA would use to determine the level of ephedrine alkaloids in a dietary supplement); the proposed label statement "Do not use this product for more than 7 days;" the proposed prohibition on labeling claims for uses that encourage long-term intake; and the proposed label statement to accompany claims for short-term uses ("Taking more than the recommended serving may cause heart attack, stroke, seizure, or death.").

We stated in our 2000 partial withdrawal of the June 1997 proposal that we continued to have a public health concern about the use of dietary supplements containing ephedrine alkaloids and that we would continue to monitor and provide appropriate followup on adverse events associated with the use of these products. We also stated that withdrawal of certain provisions of the June 1997 proposal did not limit our discretion to initiate enforcement actions with respect to dietary supplements containing ephedrine alkaloids.

On the same day as the 2000 partial withdrawal of the June 1997 proposal, we announced the availability of certain documents to update the administrative docket of the proposed rule (65 FR 17509, April 3, 2000). The documents consisted of additional information about some of the 270 adverse event reports (AERs) received by FDA between February and September 1997. In a separate **Federal Register** notice also issued on April 3, 2000, we announced the availability of additional AERs and related information received after publication of the proposed rule. The additional information included the analyses of these new AERs by experts both inside and outside the agency; review of labels of products associated with these adverse

events; review of the use of *Ephedra* species in traditional Asian medicine; analysis of the likelihood and factors affecting the reporting of adverse events; and summaries of the known physiological, pharmacological, and toxic effects of ephedrine alkaloids (Ref. 18). This announcement was made in part to prepare for a meeting convened by the U.S. Department of Health and Human Services (HHS) Office of Women's Health (OWH) in August 2000 to discuss information about the safety of dietary supplements containing ephedrine alkaloids. Shortly before that meeting, FDA announced (65 FR 46721, July 31, 2000) that it would again reopen the comment period for the June 1997 proposal from August 10, 2000 (the day after the OWH meeting) until September 30, 2000. In that notice, we also announced the availability of a report on phenylpropanolomine and hemorrhagic stroke (Ref. 19).

In April 2001, HHS's Office of the Inspector General issued a report entitled "Adverse Event Reporting For Dietary Supplements: An Inadequate Safety Valve" (Ref. 20) that assessed the effectiveness of FDA's Adverse Event Reporting System. This report found that adverse event reporting systems typically detect only a small proportion of the events that actually occur.

In the **Federal Register** of March 5, 2003 (68 FR 10417), we published a notice making available new information about dietary supplements containing ephedrine alkaloids and requesting public comment on the new information and on regulation of these products (68 FR 10417, March 5, 2003) (March 2003 notice). We specifically sought comments on whether, in light of current information, we should determine that dietary supplements containing ephedrine alkaloids are adulterated because they present a significant or unreasonable risk of illness or

injury under the conditions of use recommended or suggested in labeling or under ordinary conditions of use if the labeling is silent. The notice also sought comment on a revised version of the warning statement first proposed on June 4, 1997. The revised warning statement had two components, a short warning that would be required to appear on the principal display panel (PDP) and a longer warning that could appear elsewhere in labeling. The proposed PDP warning stated that strokes, heart attacks, seizures, and death have been reported after consumption of dietary supplements containing ephedrine alkaloids and that the risks of adverse events increase with strenuous exercise and with use of other stimulants, including caffeine. The longer proposed warning included more detailed information about risks associated with the use of the product and recommended that consumers avoid using the product and/or consult a doctor under certain circumstances.

In the March 2003 notice, we asked for public comment on all additional evidence developed since the publication of the June 1997 proposal. One such study was a report by the Southern California Evidenced Based Practice Center (the RAND report, RAND, or RAND Corp.), commissioned by the National Institutes of Health (NIH) (Refs. 21 and 22). RAND reviewed recent evidence on the risks and benefits of ephedra and ephedrine[2] and found that dietary supplements containing ephedrine alkaloids are associated with higher risks of mild to

[2] The RAND report uses the term "ephedra" to refer to ephedrine alkaloids from botanical sources, whether or not they are contained in dietary supplements. RAND uses the term "ephedrine" to refer to pharmaceutical sources of ephedrine.

moderate side effects such as heart palpitations, psychiatric effects, and upper gastrointestinal effects, and symptoms of autonomic hyperactivity such as tremor and insomnia, especially when they are taken with other stimulants. The RAND report identified 21 "sentinel events" among the adverse event reports it reviewed, including stroke, heart attack, and death.[3] RAND also found limited evidence of an effect of ephedra on short-term weight loss. Furthermore, RAND found limited evidence that synthetic ephedrine and caffeine in combination have a short-term enhancement effect on athletic performance in certain physical activities. RAND concluded that the scientific literature does not support an effect of ephedrine alone on athletic performance, and there were no clinical trials on the effects of dietary

[3] RAND defined a "sentinel event" as a case that met all three of the following criteria: (1) Documentation of an adverse event that met the selection criteria; (2) documentation that the person having the adverse event took an ephedra-containing supplement or ephedrine within 24 hours prior to the event (for cases of death, myocardial infarction [heart attack], stroke, or seizure); and, (3) documentation that alternative explanations for the adverse event were investigated and were excluded with reasonable certainty. These criteria were subject to procedures which included the following (among other procedures): medical record documentation that an adverse event had occurred; documentation that the subject had consumed ephedra or ephedrine within 24 hours prior to the adverse event, or that a toxicological examination revealed ephedrine or one of its associated products in the blood or urine. Cases with no such documentation were not reviewed further. For the Metabolife cases, ephedra was assumed to have been used within the prior 24 hours for all but psychiatric events. All cases of stroke that met the criterion of having consumed ephedra or ephedrine within 24 hours were reviewed in more detail; to be classified as a "sentinel event," reports of thrombotic stroke needed to have an assessment for a hypercoagulable state and vasculitis, reports of embolic stroke needed to have an embolic evaluation performed, and reports of hemorrhagic stroke required an examination to assess structural problems with the circulatory system of the brain.

supplements containing botanical ephedrine alkaloids on athletic performance. One of the studies reviewed by RAND, a study by Boozer, *et al.* (2002), though frequently relied on by the dietary supplement industry to demonstrate the safety of ephedrine alkaloids, raised additional concerns about the effects of dietary supplements containing ephedrine alkaloids on blood pressure. This evidence, discussed in section V.B of this document, added significantly to the evidence suggesting that dietary supplements containing ephedrine alkaloids as currently marketed are associated with unreasonable safety risks.

At about the same time as we published the March 2003 notice, we issued warning letters to 26 firms for making unsubstantiated claims concerning the use of dietary supplements containing ephedrine alkaloids to enhance athletic performance. We also issued warning letters to firms promoting dietary supplements containing ephedrine alkaloids as alternatives to illicit street drugs.

In July 2003, GAO testified at a House Subcommittee hearing on issues relating to dietary supplements containing ephedrine alkaloids. GAO's testimony discussed and updated some of its findings from its prior 1999 report on dietary supplements containing ephedrine alkaloids (Ref. 23). The testimony provided new information, including an evaluation of Metabolife International's records of health-related calls from consumers of Metabolife 356 (Ref. 24). GAO noted that the types of adverse events identified in the health-related call records from Metabolife International were consistent with the types of adverse events reported to us, as well as with the scientifically documented physiological effects of ephedrine alkaloids. GAO also noted that despite the limited information contained in most of the call records, 14,684 call records contained

reports of at least one adverse event among consumers of Metabolife 356. The GAO testimony identified 92 serious events that included heart attacks, strokes, seizures, and deaths and emphasized that these findings were similar to other reviews of the call records, including those done by Metabolife International and its consultants. The GAO testimony noted that, in those call records where age was documented, many of the serious adverse events occurred in relatively young consumers, with more than one-third being under the age of 30. Furthermore, for those call records in which quantity of use and/or frequency and duration of use were noted, most of the serious adverse events occurred among Metabolife 356 users who used the product within the recommended guidelines, i.e., they did not take more of the product nor consume it for a longer period of time than the product label recommended.

D. Petitions Received Relating to Dietary Supplement Containing Ephedrine Alkaloids

We received three petitions relating to dietary supplements containing ephedrine alkaloids. The first petition, dated August 27, 1998, was submitted by the American Obesity Association and requested that we issue a final rule on dietary supplements containing ephedrine alkaloids that adopts the regulations in the June 1997 proposal. The second petition, dated October 25, 2000, was filed jointly by the American Herbal Products Association, the Consumer Healthcare Products Association, the National Nutritional Foods Association, and the Utah Natural Products Alliance and requested that we withdraw the remaining portions of our June 1997 proposal and adopt and implement in its place an industry-developed standard for the labeling and

marketing of dietary supplements containing ephedrine alkaloids.

The third petition, dated September 5, 2001, was submitted by Public Citizen. This petition requested that we declare dietary supplements containing ephedrine alkaloids adulterated because they present a significant or unreasonable risk of illness or injury under section 402(f) of the act and ban, all production and sales of these products under section 301(a) (21 U.S.C. 331(a)) of the act. The petition also requested that we issue an advisory to stop the use of dietary supplements containing ephedrine alkaloids due to the established risks of injury.

The information cited in support of this petition included:

- Summaries of the updated numbers and types of adverse events reported to us for ephedrine-alkaloid containing dietary supplements compared to the lower incidence of the same types of adverse events reported for all other dietary supplements;

- An FDA preliminary analysis of data collected by and purchased from the American Association of Poison Control Centers (AAPCC) that showed an increase in the number of ephedrine alkaloid-related AERS from 211 in 1997 to 407 in 1999; and

- Adverse events reported to Public Citizen.

The petition also cited the known pharmacological and toxicological properties of ephedrine alkaloids, recent published articles and case reports, the fact that adverse events are invariably underreported, and the lack of any evidence of long-term benefits for the products.

We have considered the information submitted by these petitions, as well as the comments received in response to these petitions and all other information in the docket. For the reasons summarized in section I.A of this document, we have concluded that dietary supplements containing ephedrine alkaloids are adulterated.

II. Summary of Letters and Comments

We have received more than 48,000 comments in three dockets pertaining to ephedrine alkaloids, Docket Nos. 1995N-0304, 2000N-1200, and 2001P-0396. These comments include all letters received prior to the June 1997 proposal, all comments received in response to **Federal Register** notices, and all submissions related to public meetings pertaining to dietary supplements containing ephedrine alkaloids. The 48,000 comments include more than 41,000 form letters received in the 1997 docket. Many comments submitted identical or nearly identical statements to more than one docket or in response to more than one **Federal Register** notice. Most of the comments were submitted by individual consumers who use dietary supplements containing ephedrine alkaloids or by independent distributors of these products. Other comments were received from persons who had, or who knew persons who had, suffered adverse events or who were reporting adverse events associated with the use of an ephedrine alkaloid-containing dietary supplement. The remaining comments included those submitted by medical professionals, scientists, medical or scientific associations, State or local health departments, Government agencies, members of Congress, dietary supplement manufacturers, traditional Asian medicine practitioners and associations,

dietary supplement industry trade associations, public health associations, and consumer groups.

The form letters, while not submitting substantive evidence or analyses, expressed strong views about our regulation of these products. Most of these letters opposed further federal regulation of dietary supplements containing ephedrine alkaloids. More than 13,000 comments opposed a ban of these products and indicated that further restrictions on these products would infringe on personal choice. Thousands of comments requested that FDA not impose stricter regulations on dietary supplements containing ephedrine alkaloids than those imposed on OTC drugs that contain synthetic ephedrine alkaloids. Hundreds of comments requested that we not ban or reclassify ephedra as a prescription drug because, they claimed, such action would result in illegitimate profits for the pharmaceutical companies. Many expressed the view that we should only ban supplements containing excessive amounts of ephedrine alkaloids and those marketed to adolescents and children or to others who may abuse and misuse these products.

Some form letters supported further regulation of these dietary supplement products. Several stated that dietary supplements containing ephedrine alkaloids are dangerous and asked us to ban them. Others requested that we impose more stringent requirements such as mandatory warning labels and maximum dosage levels. Thousands of form letters stated that DSHEA provides us with the necessary authority to protect the public health and that we do not need additional authority. Numerous comments criticized us for failing to exercise the enforcement powers authorized by DSHEA. Numerous form letters requested that ephedrine alkaloids be allowed for

professional use by traditional Asian medicine practitioners and dispensed by licensed health care professionals.

We have also received approximately 2,500 individual comments that, although not form letters, did not contain substantive information, analyses, or data. Many of these individual comments raised the same issues as raised in the form letters. Many comments were personal testimonials of how dietary supplements containing ephedrine alkaloids are effective for weight control, improving stamina, or treating medical conditions, and should not be banned or further restricted. Several comments stated that the June 1997 proposal lacked scientific basis and that there are many legitimate studies that support the responsible use of dietary supplements containing ephedrine alkaloids; however, these comments did not submit any additional scientific evidence. Others stated that dietary supplements containing ephedrine alkaloids are safe when used appropriately. Others were personal testimonials of adverse events related to these products that urged a ban or tighter restrictions of these products. Some comments criticized the proposed label warning as too long and ineffective.

Other comments came from members of Congress, with many echoing the issues raised by the form letters. Several congressional representatives commented that Americans are increasingly turning to dietary supplements to improve their health and that Congress passed DSHEA to ensure that these products are regulated as foods rather than drugs. They cited our own statements that DSHEA gives FDA sufficient authority to remove unsafe dietary supplements from the market. Many urged us to ensure that there was ample opportunity to submit scientific evidence related to dietary supplements containing ephedrine

alkaloids. Many urged us to base our decisions on sound science and not rely too heavily on AERs. Some expressed concern about alleged FDA bias against dietary supplements containing ephedrine alkaloids. Others passed on concerns expressed by constituents about adverse health effects from these products. Several comments from members of Congress expressed concern about consumers' ability to read and properly use labels and warnings.

Many of the substantive comments submitted data and other information regarding the use of ephedrine alkaloids. Some comments contained legal analyses of DSHEA and other provisions of the act. Many comments related to provisions of the June 1997 proposal that were withdrawn in 2000 or that have become moot as a result of the action taken in this final rule and, therefore, do not require a response. Examples of moot issues are the proposed prohibition on claims that encourage long-term use and the proposed label statement that the product should not be used for more than 7 days. Other comments addressed issues outside the scope of the rulemaking (*e.g.*, comments about the diversion of ephedrine alkaloids for the illegal manufacture of methamphetamine and methcathinone) and will also not be addressed in this document.

A summary of all relevant comments and our responses to those comments follow. To make it easier to identify comments and our responses, the word "Comment," in parentheses, will appear before the comment summary and the word "Response," in parentheses, will appear before our response. We have also numbered each comment summary to help distinguish between different comment summaries. The number assigned to each comment summary is purely for organizational purposes and

does not signify the comments' value or importance or the order in which they were received.

III. Finding of Adulteration

A. What Does the Final Rule Do?

This final rule declares dietary supplements containing ephedrine alkaloids to be adulterated under section 402(f)(1)(A) of the act. We have determined that these products present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling or, if no conditions of use are suggested or recommended in labeling, under ordinary conditions of use. We are taking this action based upon the well-known and scientifically established pharmacology of ephedrine alkaloids, the peer-reviewed scientific literature about the effects of ephedrine alkaloids, published case reports of adverse events, and the adverse events reported to us that have occurred in individuals using products containing ephedrine alkaloids, particularly dietary supplements. We have concluded that dietary supplements containing ephedrine alkaloids pose a risk of serious adverse events, including heart attack, stroke, and death, and that these risks are unreasonable in light of any benefits that may result from the use of these products under their labeled conditions of use, or under ordinary conditions of use if the labeling is silent. We are not addressing the issue of whether these products present a "significant" risk under section 402(f)(1)(A) of the act.

B. What Products are Covered?

This final rule applies to dietary supplements containing ephedrine alkaloids, including, but not limited to,

those from the botanical species *Ephedra sinica* Stapf, *Ephedra equisetina* Bunge, *Ephedra intermedia* var. tibetica Stapf, *Ephedra distachya* L., *Sida cordifolia* L. and *Pinellia ternata* (Thunb.) Makino or their extracts. The ingredient sources of the ephedrine alkaloids include raw botanicals and extracts from botanical sources. Although synthetic ephedrine (in the form of ephedrine hydrochloride) has been found in products labeled as dietary supplements, ephedrine hydrochloride was approved for use as a human drug as early as the late 1940s and, to the best of our knowledge there is no evidence that it was marketed prior to that time as a dietary supplement or food. Furthermore, ephedrine hydrochloride and other synthetic sources of ephedrine cannot be dietary ingredients because they are not constituents or extracts of a botanical, nor do they qualify as any other type of dietary ingredient. For these reasons, products containing synthetic ephedrine cannot be legally marketed as dietary supplements (*See* section 201(ff)(1) and 201(ff)(3)(B) of the act (21 U.S.C. 321(ff)(1) and (ff)(3)(B))). In October 2001, we brought a seizure action against $2.8 million worth of finished drug products containing synthetic ephedrine hydrochloride that were labeled as dietary supplements (*United States* v. *1009 Cases * * * E'ola International AMP II*), No. 2:01CV-820C (D. Utah filed October 22, 2001)). As a result of this seizure, in 2002, the manufacturer signed a consent decree agreeing to the condemnation and destruction of the seized products and prohibiting it from manufacturing or distributing violative ephedrine hydrochloride products. In other actions, we have sent warning letters to multiple firms that were marketing products containing synthetic ephedrine alkaloids as dietary supplements, resulting in the removal of the illegal products from the market.

The final rule does not apply to conventional food products that contain ephedrine alkaloids. Substances intentionally added to a conventional food are generally considered to be food additives under section 201(s) of the act. Ephedrine alkaloids contained in conventional foods would generally be considered unsafe food additives (*see* section 409 of the act (21 U.S.C. 348)). A food that contains an unsafe food additive is adulterated under section 402(a)(2)(C) of the act.

This final rule also does not include OTC or prescription drugs that contain ephedrine alkaloids. The use of ephedrine or pseudoephedrine for the treatment of asthma, colds, allergies, or any other disease is beyond the scope of this final rule. Ephedrine is allowed as an active ingredient in oral OTC bronchodilator drugs for use in the treatment of medically diagnosed mild asthma (Sec. 341.16 (21 CFR 341.16)), when used within the established dosage limits and when the product is labeled in accordance with the required statements of identity, indications, warnings, and directions for use found in Sec. 341.76. In the near future, we intend to propose revisions to Sec. 341.76 to reflect current scientific information about the risks of ephedrine. Both ephedrine (topical) and pseudoephedrine (oral) are permitted as active ingredients for use as nasal decongestants (Sec. 341.20), when they are used within the dosage limits established by and labeled in accordance with Sec. 341.80. The topical use of ephedrine will not be further discussed in this rule because it is not relevant to oral consumption of ephedrine in dietary supplements. The use of ephedrine alkaloids in drug products is discussed in more detail in section V.B.3 of this document.

Several *Ephedra* species (including those known as ma huang) have a long history of use in traditional Asian medicine. These products are beyond the scope of this rule because they are not marketed as dietary supplements. The use of ephedrine alkaloids in traditional Asian medicine is discussed in more detail in section V.B.5 of this document. As we describe there, this rule does not change how these products are regulated under the act.

(Comment 1) One comment stated that we coined the term "ephedrine alkaloids" to improperly broaden the scope of the published scientific literature and AERs cited in the June 1997 proposal. The comment pointed out that ephedrine, pseudoephedrine, and phenylpropanolamine (PPA) are all different chemical entities and stated the opinion that only data on ephedrine are relevant to the June 1997 proposal.

(Response) Although we agree that the terms ephedrine, pseudoephedrine, and PPA refer to different chemical entities, we disagree with the rest of the comment and its conclusions. The term "ephedrine alkaloids" refers to a class of naturally occurring compounds structurally related to ephedrine, and the term has been used in that manner in the scientific literature (Refs. 25 and 26). We chose this particular term, rather than several alternatives, such as "*Ephedra* bases" and "ephedrine type alkaloids," to limit the scope of the June 1997 proposal to those compounds that are natural constituents of the aerial parts of the *Ephedra* plant or other botanical sources of ephedrine and related alkaloids. We also defined the term by listing the six principal natural alkaloids in the June 1997 proposal and other FDA documents (Refs. 6 and 27). The ephedrine alkaloids in botanicals include l-ephedrine, d-pseudoephedrine, l-norephedrine, l-methylephedrine,

d-norpseudoephedrine, d-methylpseudoephedrine, and minor related alkaloids. All of these compounds are pharmacologically active substances in the plant. Therefore, we considered all of them in our evaluation of the risks associated with the use of the botanical or extracts from the botanical. However, as discussed in the response to comment 24 in section VI.B.1 of this document, we recognize that there are some differences between ephedrine and PPA.

(Comment 2) Several comments asked whether North American species of *Ephedra* (*e.g.*, Mormon Tea) are covered in this rulemaking.

(Response) Most North American species of *Ephedra* (*e.g.*, Mormon tea) do not contain ephedrine alkaloids (Refs. 2 and 26). Nonetheless, any dietary supplement that contains ephedrine alkaloids from any botanical source, including from a North American species of Ephedra, is subject to this rulemaking.

IV. Legal Issues

A. What Is Our Legal Authority Under the Act?

We are issuing this final regulation under sections 402(f)(1)(A) and 701(a) of the act (21 U.S.C. 371(a)). Section 402(f)(1)(A) of the act deems a food to be adulterated for the following reasons:

If it is a dietary supplement or contains a dietary ingredient that –

(A) presents a significant or unreasonable risk of illness or injury under –

(i) conditions of use recommended or suggested in labeling, or

(ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use.

This regulation makes a finding that dietary supplements containing ephedrine alkaloids are adulterated because they present an unreasonable risk within the meaning of section 402(f)(1)(A) of the act. This finding is based on our conclusion that the risks of these products outweigh their benefits. Our legal interpretation of "unreasonable risk" is discussed in detail in section V.D.1 of this document. This regulation does not address the meaning of "significant risk" or whether dietary supplements containing ephedrine alkaloids present a significant risk under section 402(f)(1(A) of the act.

Section 701(a) of the act gives FDA authority to issue regulations for the efficient enforcement of the act. We are using this rulemaking authority for dietary supplements containing ephedrine alkaloids because we are articulating a standard for unreasonable risk under 402(f)(1)(A) of the act for the first time and because it is more efficient to declare these products adulterated as a category than to remove them from the market in individual enforcement actions in which we would have to establish, for each individual product, that they present a significant or unreasonable risk.

The March 2003 notice asked about the adequacy of FDA's authority to regulate dietary supplements containing ephedrine alkaloids. More specifically, we sought comments on "what additional legislative authorities, if any, would be necessary or appropriate to enable us to

address this issue most effectively" (68 FR 10417 at 10420).

(Comment 3) Many comments expressed the view that we already have the authority we need to take action against dietary supplements containing ephedrine alkaloids. These comments cited our authority to declare these supplement products to be a significant or unreasonable risk or imminent hazard under section 402(f)(1) of the act or to regulate the products as containing a poisonous or deleterious substance that may render them injurious to health under section 402(a). The comments differed as to whether we had the necessary evidence to utilize these provisions. Several comments opposed any additional authority and criticized us for allegedly not fully implementing the authority we already have.

(Response) We agree that we have the authority to take action against dietary supplements that contain ephedrine alkaloids. All three authorities mentioned by the comments are available to us when circumstances warrant. In this instance, we have chosen to proceed under the adulteration standard in section 402(f)(1)(A) of the act. We believe that we have sufficient evidence to meet this standard.

(Comment 4) In contrast, other comments stated that our legal authority should be strengthened. Several comments expressed the view that DSHEA needs to be amended because it cannot adequately protect public health. One public interest group noted that our delay in acting reflects the difficulty we encounter implementing DSHEA. Several comments offered suggestions for amendments that would strengthen our legal authority, including mandatory reporting of adverse events, certain sales

restrictions (*e.g.*, restricting sales to behind the counter only, prohibiting sales to individuals under the age of 18), special labeling requirements for dietary supplements containing ephedrine alkaloids, registration and listing, premarket approval for safety and efficacy (particularly for all new stimulants and steroid substitutes), and repeal of the *de novo* review provision so that we would receive judicial deference on adulteration issues. A few comments suggested that dietary supplements be regulated as drugs. One comment suggested new legislation to classify dietary supplements according to a risk-based regulatory scheme.

(Response) We must regulate dietary supplements under our existing authority. Accordingly, we are unable to take action regarding suggestions for amendments to DSHEA because any such amendments must result from congressional action rather than rulemaking. Therefore, we are not addressing those suggestions in this rule.

(Comment 5) One comment stated that conventional food safety standards, i.e., the generally recognized as safe (GRAS) standard or the standard for FDA approval as a food additive, do not apply to dietary ingredients.

(Response) We agree that the standards referred to in this comment do not apply to dietary ingredients. Premarket approval is required of substances that are food additives as defined in section 201(s) of the act. Substances that would otherwise fall under the food additive definition but are generally recognized as safe by experts are not food additives and do not require premarket approval. Dietary ingredients contained in, or intended for use in, a dietary supplement are explicitly excluded from the food additive definition in section 201(s)(6) of the act. Therefore, neither the premarket approval regime for food

additives nor the GRAS standard applies to dietary ingredients. We are instead basing this final rule on the dietary supplement adulteration standard set forth in section 402(f)(1)(A) of the act.

(Comment 6) One comment stated we are violating the First Amendment of the U.S. Constitution and the Administrative Procedure Act (APA) by requiring a much higher standard of safety for dietary supplements than for conventional foods. Another comment also raised concerns about the First Amendment limits of FDA's authority to regulate dietary supplements containing ephedrine alkaloids.

(Response) We disagree with these comments. There are a number of different safety standards for foods (*see, e.g.*, section 402(a)(1) and section 402(a)(2)(C) of the act), and whether these standards are higher or lower than the "significant or unreasonable risk" standard for dietary supplements in section 402(f)(1)(A) of the act is not relevant to the legal sufficiency of this rule. To the extent that we regulate dietary supplements and conventional foods differently, these differences are justified by the differences in the statutory provisions that apply to these two categories of products. Although some parts of the act apply to both dietary supplements and conventional foods, other provisions apply only to one or the other. Where Congress expressly provided for dietary supplements to be subject to a requirement or standard that does not apply to conventional foods, we may implement that provision without violating the APA. Further, this final rule does not violate the First Amendment. This rule does not restrict speech; rather, it makes a finding of adulteration that results in a prohibition on the distribution and sale of a product that presents unreasonable health risks. Such

restrictions on purely commercial, nonexpressive conduct are not subject to First Amendment scrutiny. *See, e.g., United States* v. *O'Brien*, 391 U.S. 367, 376 (1968).

(Comment 7) Several comments expressed the view that these products should be regulated as drugs under our existing authority. Some comments stated that we should make these products available only by prescription, arguing that the potential health hazards associated with dietary supplements containing ephedrine alkaloids are too serious for OTC use and that restricting access by requiring a prescription would insert trained medical professionals into a case-by-case decision on the appropriateness of these products to an individual consumer. Further, one comment recommended that if the frequency of adverse events under prescription status does not improve, more restrictive action should be implemented, including the withdrawal of all products containing ephedrine alkaloids from the market.

(Response) We do not agree that all dietary supplements containing ephedrine alkaloids may be regulated as drugs under our existing authority. Products are drugs only if they meet the definition of drug in section 201(g)(1) of the act. Products containing ephedrine alkaloids are regulated as drugs if they are intended to be used in the diagnosis, cure, mitigation, treatment, or prevention of disease (section 201(g)(1)(B) of the act). Without evidence of intended use for such purposes, the product is not a drug under the act. Some dietary supplements containing ephedrine alkaloids are promoted for disease uses, *e.g.*, to treat obesity. In such instances, we can and have taken action against certain dietary supplement products as drugs. Under the act, considerations such as potential risks to health, need for medical supervision, and pharmacology

of a product that meets the dietary supplement definition are not by themselves sufficient to subject the product to regulation as a drug.

To the extent that comments suggest that these products could somehow remain dietary supplements but be available only by prescription, we note that we do not have authority to take such action. The act gives us the authority to restrict drugs and devices to prescription use; it does not give us the authority to restrict dietary supplements to prescription use.

(Comment 8) One comment stated that the generally accepted definition of safety for a drug, i.e., a low incidence of adverse reactions or significant side effects under appropriate conditions of use, and a low potential for harm, which might result from abuse situations, is equally applicable to dietary supplements or food.

(Response) We do not agree that the safety standards for drugs apply to dietary supplements or other foods. As explained previously, dietary supplements are not drugs unless they meet the definition of drug in section 201(g)(1) of the act. The same is true for conventional foods. We are basing this final rule on the dietary supplement adulteration standard set forth in section 402(f)(1)(A) of the act. The adulteration standard for dietary supplements set forth in section 402(f)(1)(A) of the act implies a risk-benefit calculus. While we also use a risk-benefit evaluation in the drug evaluation process (*see* Sec. 312.21(c), Sec. 314.50(c)(5)(viii), and Sec. 330.10(a)(4) (21 CFR 312.21(c), 314.50(c)(5)(viii), and 330.10(a)(4))), the act creates different evidentiary standards for dietary supplements and drugs. Therefore, we are not applying the drug safety standard to dietary supplements.

B. Do the Ephedrine Alkaloid-Containing Products Covered by this Rule Fall Within the Definition of Dietary Supplement Under the Act?

A threshold issue is whether the products covered by this rule meet the definition of a dietary supplement under section 201(ff) of the act.

(Comment 9) One comment from a State department of health stated the opinion that dietary supplements containing ephedrine alkaloids present significant risks when they are consumed as a regular part of the diet and do not fall within section 201(ff)(1) of the act. The comment explained that because these products cannot be used on a daily basis without presenting significant risks they cannot be "intended to supplement the diet" and are not dietary supplements within the meaning of the act. A related comment expressed the opinion that, for a substance to be a dietary supplement, it must be proven that the human body needs the substance to establish a need for supplementation.

(Response) We agree with these comments in part and disagree in part. We agree that dietary supplements containing ephedrine alkaloids present a risk when consumed as a regular part of the diet; as discussed in section V.B of this document, they present a risk to some users even when consumed occasionally. We do not agree, however, that dietary supplements containing botanical ephedrine alkaloids do not fall within the definition of a dietary supplement in section 201(ff) of the act. Section 201(ff)(1) of the act, added by DSHEA, provides, in part, that the term "dietary supplement" means a product "intended to supplement the diet" that bears or contains one or more dietary ingredients. Among the dietary ingredients listed in section 201(ff)(1) of the act are herbs and

other botanicals. Therefore, botanical sources of ephedrine alkaloids, such as *Ephedra sinica* Stapf and the other botanicals described in section III.B. of this document, are dietary ingredients. Further, we do not agree that the phrase "intended to supplement the diet" authorizes the exclusion of a product from the dietary supplement definition solely on the basis of risk. Given the explicit references to risk in section 402 of the act and the inclusion of botanicals as a category of dietary ingredients in section 201(ff)(1) of the act, it seems clear that Congress intended us to regulate botanical products as dietary supplements (provided that they are not drugs and otherwise meet the dietary supplement definition) and to evaluate their risks under the adulteration provisions in section 402 of the act.

We also do not agree that, under the dietary supplement definition, it must be proven that the human body needs a particular substance to establish a need for supplementation. Under DSHEA, a substance does not necessarily have to be shown to be essential to human nutrition to be marketed as a dietary supplement. Although no provision in the act or legislative history directly addresses this issue, section 201(ff) of the act lists classes of dietary ingredients (*e.g.*, botanicals) that are not essential for growth or to maintain good health (Ref. 28). The fact that Congress classified such substances as dietary ingredients is clear evidence that Congress did not intend to limit dietary ingredients to substances that have been deemed to be essential in human nutrition.

(Comment 10) Several comments, including one from an industry medical consultant, stated that herbal products should not be regulated under DSHEA because they have physiologic effects and significant potential for toxicity. The

comment encouraged us to work with industry to establish an appropriate regulatory category for botanicals.

(Response) Under the act (as amended by DSHEA), botanicals can be marketed as dietary supplements provided that they otherwise meet the dietary supplement definition, and are safe and properly labeled. If botanicals meet the drug definition in section 201(g) of the act, they are properly regulated as drugs. In this regard, we published a final rule entitled "Additional Criteria and Procedures for Classifying Over-the-Counter Drugs as Generally Recognized as Safe and Effective and Not Misbranded" (67 FR 3060, January 23, 2002). This rule defines the term "botanical drug substance" and explains how to submit a time and extent application to request that a botanical drug substance be included in an OTC drug monograph (*see* Sec. 330.14). In addition, we recognize, and are addressing, the current need for guidance for manufacturers seeking to develop botanicals as either OTC or prescription drug products under the applicable statutory and regulatory requirements. (*See* Guidance for Industry: Botanical Drug Products (Draft Guidance) (August 2000) (available at http://www.fda.gov/cder/guidance/1221dft.pdf).)

C. Administrative Procedures

(Comment 11) Several comments stated that it is premature to request comments on whether dietary supplements containing ephedrine alkaloids present a significant or unreasonable risk before we define that standard. These comments urged us to undertake a rulemaking, or a guidance document, on this new standard so that it can be applied in the future to all dietary supplements posing

health concerns. One comment suggested that defining "significant or unreasonable risk" may require new legislation.

(Response) We do not agree that we must define the term "unreasonable risk" standard through regulation or guidance before taking action against dietary supplements containing ephedrine alkaloids based upon this standard. An agency may interpret a statutory provision through rulemaking or case-by-case adjudication (*SEC* v. *Chenery*, 332 U.S. 194 (1947)). We conclude, based upon available evidence discussed in section V of this document, that dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury because their risks outweigh their benefits, and that these products are therefore adulterated under section 402(f)(1)(A) of the act. We are using our general rulemaking authority to issue regulations for the efficient enforcement of the act (section 701(a) of the act) to issue a regulation applying the standard in the context of a particular category of dietary supplements – those that contain botanical ephedrine alkaloids. We are not required to issue a separate rule or guidance defining the 402(f)(1)(A) standard before issuing such a regulation. Similarly, lack of a regulation or guidance defining the standard neither prevents us from taking enforcement action against dietary supplements that present an "unreasonable risk," nor is it new legislation necessary for us to interpret the meaning of "unreasonable risk." If Congress has clearly spoken to a question of statutory interpretation, the agency charged with administering the statute must implement the unambiguous intent of Congress ("*Chevron* step one") (*Chevron U.S.A., Inc.* v. *Natural Resource Defense Council*, 467 U.S. 837, 842-843 (1984)). If a statute is silent or ambiguous on

the question, however, the agency may interpret the ambiguous provision ("*Chevron* step two") *Id.* at 843-844. When such administrative interpretations are made through rulemaking, they will be upheld as long as they are reasonable and consistent with the statute's purpose and legislative history (*Christensen* v. *Harris County*, 529 U.S. 576, 587 (2000); *Chevron U.S.A., Inc.* v. *FERC*, 193 F.Supp.2d 54, 68 (D.D.C. 2002)). As discussed in the response to comment 59 in section V.D.1 of this document, we have concluded under *Chevron* step one that the phrase "unreasonable risk" clearly directs FDA to conduct a risk-benefit analysis. Even if a court were to find that phrase ambiguous, however, our interpretation is reasonable under *Chevron* step two.

(Comment 12) Several comments urged us not to act against all dietary supplements containing ephedrine alkaloids because all such products are different and must be considered individually. The comments cited differences in dosages, formulations, labeling, etc., across products and, thus, each product must be analyzed on its own merits. One industry comment argued that we exceeded our statutory authority in trying to regulate all dietary supplements containing ephedrine alkaloids through notice and comment rulemaking.

(Response) We do not agree that we may not regulate the entire category of dietary supplements containing ephedrine alkaloids through rulemaking. We recognize that there are differences between different dietary supplements containing ephedrine alkaloids. However, we conclude, based on available science, that all dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury, regardless of how they are formulated or labeled, because the risks outweigh

any benefits that may result from use of the products. Therefore, we may issue a rule finding the entire class of products adulterated.

(Comment 13) A few comments noted that we bear the burden of proof to show dietary supplements are adulterated under section 402(f)(1) of the act.

(Response) We agree with this comment. Section 402(f)(1) of the act clearly states that in any proceeding under that provision, "the United States shall bear the burden on each element to show that a dietary supplement is adulterated." We have met that burden in this rulemaking.

(Comment 14) Several comments discussed our ability to declare dietary supplements containing ephedrine alkaloids an imminent hazard under section 402(f)(1)(C) of the act.

(Response) We are not addressing these comments because we have chosen to proceed under section 402(f)(1)(A).

(Comment 15) One industry comment stressed that comments to the June 1997 proposal may not be used to authorize other final regulations. The comment expressed concern that comments to a proposed warning statement would be used as a basis for another FDA action to regulate these supplements.

(Response) We disagree with this comment. FDA may issue this final regulation based on a finding that dietary supplements containing ephedrine alkaloids are adulterated because they present an unreasonable risk under section 402(f)(1)(A) of the act. APA requires agencies to provide the public with notice and an opportunity for

comment before issuing a new regulation (5 U.S.C. 553(b) and (c)). In keeping with this requirement, a final rule may differ from a proposed rule if the final rule is a "logical outgrowth" of a proposed rule *(Small Refiner Lead Phase-Down Task Force* v. *EPA*, 705 F.2d 506, 547 (D.C. Cir. 1983)). The inquiry into whether a final rule is a logical outgrowth of the proposed rule is often stated as whether the regulated party "should have anticipated that such a requirement might be imposed" (*Small Refiner*, 705 F.2d at 549). Agencies "undoubtedly have authority to promulgate a final rule that differs in some particulars from its proposed rule* * * '[a] contrary rule would lead to the absurdity that * * * the agency can learn from the comments on its proposals only at the peril of starting a new procedural round of commentary'" (*Small Refiner*, 705 F.2d at 546-547 (quoting *International Harvester Co.* v. *Ruckelshaus*, 478 F.2d 615, 632 n.51 (D.C. Cir.1973))). The D.C. Circuit has also stated: "The APA notice requirement is satisfied if the notice fairly apprises interested person of the subjects and issues the agency is considering; 'the notice need not specifically identify "every precise proposal which [the agency] may adopt as a final rule"' (*Chemical Manufacturers Association Waste Mfrs.* v. *EPA*, 870 F.2d 177, 203 (5th Cir. 1989) (quoting *United Steelworkers of Am.* v. *Schuylkill Metals*, 828 F.2d 314, 317 (5th Cir. 1987) (internal citations omitted))).

Our June 1997 proposal, along with our March 5, 2003 **Federal Register** notice, provided a sufficient basis to allow the public to anticipate our actions in this final rule. Through our proposed actions on dietary supplements containing ephedrine alkaloids, the public was properly notified of the possibility that we would find such products to be adulterated under section 402(f)(1)(A) of the act. In

fact, our March 2003 notice specifically asked for comment on whether dietary supplements containing ephedrine alkaloids present a significant or unreasonable risk under section 402(f)(1)(A) of the act. We also sought comment on new evidence concerning the safety of dietary supplements containing ephedrine alkaloids (68 FR 10417 at 10420). In addition, the restriction on ephedrine alkaloid/stimulant combinations proposed in 1997, which was unaffected by the 2000 partial withdrawal proposal, was based in part on a finding of adulteration under section 402(f)(1)(A) of the act (62 FR 30678 at 30696). Though we did not specifically propose to codify a finding of adulteration based on significant or unreasonable risk in the March 2003 notice, it was clear that we were contemplating the possibility that dietary supplements containing ephedrine alkaloids were adulterated under section 402(f)(1)(A) of the act. Courts have upheld final rules that contained new elements when the public was made aware that the agency was contemplating such a change (*See Chem. Mfrs. Ass'n.*, 870 F.2d 202-203). Furthermore, we received several comments regarding the possibility of a finding that all dietary supplements containing ephedrine alkaloids would be deemed adulterated under section 402(f)(1)(A) of the act. Though not determinative of logical outgrowth in and of themselves, comments on the issue are evidence that the public received adequate notice of our final rule (*Shell Oil Co.* v. *EPA*, 950 F.2d 741, 757 (D.C. Cir. 1991)). Based upon our explicit request for comments on the adulteration issue in our March 2003 notice, our reference to the section 402(f)(1)(A) of the act adulteration standard as a basis for our June 1997 proposal, and the fact that a number of parties commented on whether dietary supplements containing ephedrine alkaloids present a significant

or unreasonable risk, there was adequate notice to the public of our actions in this final rule.

(Comment 16) Several comments cited language in section 402(f)(1) of the act providing that courts must review any determination under section 402(f)(1) of the act *de novo* and further stated that we would not get judicial deference in any court review. The comments argued that, under this provision, it would make no difference whether we brought our case initially in court or whether we proceeded through rulemaking that was subsequently challenged in court. One trade association noted that such *de novo* review is a novel approach in that usually a court would just review the administrative record.

(Response) Section 402(f)(1) of the act states that a court will decide any issue under that paragraph on a *de novo* basis. We agree that the *de novo* standard of review applies to our factual findings under section 402(f)(1) of the act, but do not agree that it applies to our conclusion under *Chevron U.S.A., Inc.*, that "unreasonable risk" means a risk-benefit analysis (*see* section V.D.1 of this document). This interpretation of the *de novo* provision of section 402(f)(1) of the act is consistent with case law on the *Toxic Substances Control Act* (TSCA), which contains an unreasonable risk standard coupled with a "substantial evidence" standard of review, analogous to the act's unreasonable risk standard coupled with a *de novo* standard of review. In *Chem. Mfrs. Ass'n* v. *EPA*, 859 F.2d 977 (D.C. Cir. 1988), the D.C. Circuit distinguished EPA's legal interpretation of unreasonable risk, which received deference under *Chevron U.S.A., Inc.* v. *Natural Resources Defense Council*, 467 U.S. 837 (1984), from its burden of showing with "substantial evidence" in the record that it has met the standard. The court stated: "This fairly

rigorous standard of record review should not * * * be confused with the substantive statutory standard * * * " (859 F.2d at 992). Thus, the court in *Chem. Mfrs. Ass'n.* held that the "substantial evidence" standard of record review applied to the factual basis of EPA's decision but not to its interpretation of the statutory standard. In applying *Chevron U.S.A., Inc.*, we have concluded that Congress unambiguously intended that unreasonable risk entails a risk-benefit calculus. If a court were to find the phrase "unreasonable risk" ambiguous, however, our interpretation of unreasonable risk as meaning a risk-benefit calculus should receive *Chevron U.S.A., Inc.* deference, like EPA's interpretation of the statutory standard in *Chem. Mfrs. Ass'n.* The requirement for *de novo* review should be applied only to the factual basis of FDA's determination.

Regardless of which standard applies, however, our determination that dietary supplements containing ephedrine alkaloids present an unreasonable risk under section 402(f)(1)(A) of the act should be sustained by a court. Our conclusion that "unreasonable risk" entails a risk-benefit analysis is consistent with the express intent of Congress. The scientific evidence regarding the pharmacology of products containing ephedrine alkaloids, clinical studies showing that these products raise blood pressure, published case reports, and AERs, when compared with the evidence regarding the very modest benefits conferred by these supplements, forms a strong factual basis for finding that the known and reasonably likely risks of dietary supplements containing ephedrine alkaloids outweigh the known and reasonably likely benefits of these products. Therefore, dietary supplements containing

ephedrine alkaloids present an unreasonable risk of injury or illness under section 402(f)(1)(A) of the act.

(Comment 17) One comment submitted by a trade association noted that, before requesting the Department of Justice to take any civil action against dietary supplements containing ephedrine alkaloids, we must give appropriate notice and opportunity to present oral and written arguments at least 10 days prior to the request.

(Response) We agree with this comment in part and disagree in part. Section 402(f)(2) of the act provides that "the person against whom such proceeding would be initiated" must be given notice and the opportunity to present views, orally and in writing, 10 days before we report a violation of section 402(f)(1)(A) of the act (the "significant or unreasonable risk" provision) to the Department of Justice for a civil proceeding. By the plain language of this provision, it applies to proceedings against persons, not to proceedings against products. Thus, the requirement applies to injunction actions, which are brought against a corporate or individual person, but not to seizures, which are brought against a product. Therefore, if we were to refer a seizure of dietary supplements containing ephedrine alkaloids to the Department of Justice, the notice requirement would not apply. We further note that the current proceeding is a rulemaking, not a civil action being referred to the Department of Justice, and therefore the 10-day notice requirement does not apply.

(Comment 18) One industry comment stated that the stringent 30-day timeframe allowed for comments in response to the March 2003 notice did not provide the industry with a fair opportunity to review the administrative record and fairly respond to "any alleged new evidence

and analyses" by FDA. This comment urged us to allow for a comment period of 180 days. The comment stated that this procedural lapse would render the entire rulemaking process arbitrary and capricious.

(Response) We disagree with this comment. We believe that the 30-day comment period on the March 2003 notice provided interested persons with an adequate opportunity for review and comment. The information placed in the public docket at that time was limited, consisting of the RAND report plus six recent studies. APA requires only that an agency "give interested persons an opportunity to participate in the rulemaking through submission of written data, views, or arguments * * *" This opportunity to participate is all that the APA requires. There is no statutory requirement concerning how many days we must allow for comment, nor is there a requirement that we extend the comment period at the request of an interested person (*See Phillips Petroleum Co.* v. *EPA*, 803 F.2d 545, 559 (10th Cir. 1986)). Moreover, given that we first opened a docket on the issue of dietary supplements containing ephedrine alkaloids in 1995 and sought comments on this issue several times between then and 2003 (*see* section I.C of this document), there has been ample opportunity for all those interested to submit information and views.

V. Scientific Evaluation

A. How Did We Evaluate the Evidence?

To determine whether a dietary supplement presents an unreasonable risk of illness or injury, the agency performs a risk/benefit analysis to ascertain whether the risks of the product outweigh its benefits.

The risks and benefits of a dietary supplement must be evaluated in light of the claims and directions for use in the product's labeling or, if the labeling is silent, under ordinary conditions of use (section 402(f)(1)(A) of the act). Labeling claims for dietary supplements must be substantiated. Unless the manufacturer has substantiation that a labeling claim promoting a dietary supplement for a purported benefit is truthful and non-misleading, the claim misbrands the product (*See* section 403(a)(1) and 403(r)(6) of the act. We note that the standards for substantiating the efficacy of a drug for a labeled indication (i.e., the generally recognized as effective (GRAE) standard for OTC monograph ingredients and the substantial evidence standard for new drugs) do not apply to dietary supplements.

Substantiation of a benefit may not be necessary to lawfully market a dietary supplement if its labeling does not include a claim, and the product poses little or no risk. In weighing risks and benefits to determine whether dietary supplements containing ephedrine alkaloids present an unreasonable risk under section 402(f)(1)(A) of the act, we considered only known and reasonably likely benefits, not speculative benefits. A reasonably likely benefit is one that is supported by a meaningful totality of the evidence, given the current state of scientific knowledge, though the evidence need not necessarily meet the approval standard for a prescription drug.

Although Congress placed the burden on FDA to show "unreasonable risk," once a danger is identified, we do not believe that Congress intended us to delay action until double-blind, placebo-controlled clinical studies could be conducted or that no action be taken if such clinical studies are infeasible or unethical (*see* the response to

comment 19 of this document). While such studies are the "gold standard" for determining effectiveness, they are not always available for dietary supplements because DSHEA does not require companies to conduct such studies before marketing a dietary supplement. DSHEA also does not require postmarketing safety and adverse event reporting from dietary supplement manufacturers. Accordingly, FDA is relying on the available scientific data and literature to support its conclusion that dietary supplements containing ephedrine alkaloids present an "unreasonable risk." The government's burden of proof for "unreasonable risk" can be met with any science-based evidence of risk and does not require a showing that the substance has actually caused harm in particular cases.

For example, there is clear scientific evidence that a sustained increase in blood pressure increases the risks of cardiovascular disease (Refs. 29, 29a, and 30). Thus, a dietary supplement that caused a sustained rise in blood pressure across the population would increase the risk of cardiovascular events including stroke, heart attack, or death to that population. Even risks that may not be detectable in small studies or studies of short duration (which are not designed to detect such risks at a statistically significant level) could, over time, and on a population-wide basis, result in thousands of adverse health events.

In making a determination, we consider studies using closely related products. In considering the risks of a product, such as dietary supplements containing ephedrine alkaloids, it is appropriate to consider the safety of closely related products, such as those with the same active ingredient (*e.g.*, synthetic ephedrine products) or closely related ingredients (such as other sympathomimetics) because we would expect that dietary supplements

containing ephedrine alkaloids will exhibit pharmacological effects similar to those other products and, therefore, pose similar risks. It is more difficult to extrapolate conclusions regarding the benefits between an ephedrine drug product and a dietary supplement containing ephedrine alkaloids since the ephedrine drug product is a well defined product with a known dose of ephedrine, while in the latter there is a complex mixture with, possibly, an unknown quantity of ephedrine plus other ephedrine alkaloids, and sometimes other active ingredients, many of which may not be fully characterized. We would need to know how the two products compare with regard to systemic delivery of ephedrine (*e.g.*, the pharmacokinetics profile) to make any judgments about comparable benefits of the two products. If ephedrine pharmacokinetics were the same in a synthetic and plant-derived product and there were no ingredients or components other than ephedrine, one might conclude that the plant-derived and synthetic products would behave similarly. In actual fact, that is not the case because plant derived ephedra products contain other ephedrine alkaloids in addition to ephedrine itself (*e.g.* pseudoephedrine, methylephedrine, and others listed in section I.B of this document). Moreover, if there were other active and inactive ingredients in the plant-derived product, their properties would need to be explored.

In evaluating whether dietary supplements containing ephedrine alkaloids present an unreasonable risk, we looked at the seriousness of the risks and the quality and persuasiveness of the totality of the evidence to support the presence of those risks. We then weighed the risks against the importance of the benefits and the quality and persuasiveness of the totality of the evidence to support

the existence of those benefits. We give more weight to benefits that improve health outcomes, especially in the long term, than to benefits that are temporary or rely on subjective measures such as feeling or looking better. For example, sustained, long-term weight loss in an obese or overweight person is a much more important benefit than short-term weight loss because long-term weight loss in these individuals reduces the risk of serious morbidity and mortality (*e.g.*, heart attacks and strokes), while short-term weight loss does not.

In sections V.B, C, and D of this document, we describe the evidence FDA evaluated to reach its determination that dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury.

(Comment 19) Many comments stated that any assessment of unreasonable risk must be based on sound science. Several comments stated that a conclusion about the safety and efficacy of dietary supplements containing ephedrine alkaloids is premature and that additional prospective or retrospective case controlled studies are needed to determine causality. A few comments recommended that FDA, NIH, or other parts of the federal government conduct such research to address unresolved issues of causation. Another trade association urged the government to collaborate with industry to design future controlled studies. Several of these comments cited RAND in support of the need for further research. Several comments noted that the National Center for Complementary and Alternative Medicine/NIH Working Group evaluated the RAND report and suggested a multi-site case-control study to assess the risks associated with these products, although it stated that such a study would take 4 to 8 years and cost $2 to $4 million per year (Ref. 31).

In contrast, several comments asserted that conducting clinical trials of ephedrine alkaloids would be unethical in light of the risks to the human subjects. A professional association stated that FDA regulations that govern drug development and approval would not allow such research, given the absence of information to suggest a benefit that would outweigh the risks. A few comments suggested that any study that could be approved by a human subjects committee would be required to exclude patients at risk and therefore, would not be useful in evaluating risk when the products are taken by the general population without medical supervision. Other comments expressed concern that the additional research recommended by RAND would delay efforts or render it virtually impossible to safeguard public health.

(Response) We recognize the value of properly conducted clinical trials to answer questions regarding the safety and effectiveness of FDA-regulated products. It is not clear, however, that clinical trials to evaluate the adverse effects of ephedrine alkaloids can be conducted. It would not be ethical to study the arrhythmogenic potential of ephedrine alkaloids in patients with coronary artery disease, the adverse effects of ephedrine alkaloids in people with heart failure, or the consequences of raising blood pressure in various populations. Moreover, there is now sufficient evidence, generated through multiple sources, including clinical trials, published literature, and other information, to reach the conclusion that dietary supplements containing ephedrine alkaloids have effects on blood pressure and other pharmacological risks that predict adverse effects in users. After considering the best available information, we conclude that these products present an unreasonable risk because the benefits that

may result from use of these products are outweighed by the risks associated with such use (*see* discussion in section V.D of this document). Because of the nature of these risks, we do not believe it is appropriate to delay action until further clinical studies can be conducted to evaluate the safety of dietary supplements containing ephedrine alkaloids in the general population. We would, however, support the conduct of clinical investigations (carried out under the Investigational New Drug (IND) regulations with careful screening to exclude subjects at risk and careful safety monitoring during the trials) that examine the safety and efficacy of ephedrine alkaloids, with or without caffeine, as drugs such as for the treatment of obesity (*see* 21 CFR part 312).

(Comment 20) Two comments stated that there is an accepted scientific methodology for determining whether, and at what level, a food additive, dietary ingredient, OTC or prescription drug, or biologic may be hazardous to human health. The stated components of this methodology include reviews of the following reports: (1) The existing scientific literature on the substance, to determine what is known about the substance's risk, particularly at the levels to be used in a product; (2) clinical studies involving the substance; (3) available animal studies on the substance and, if necessary, the conduct of additional studies; and (4) adverse event reports caused by the substance.

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major alkaloid in most dietary supplements containing ephedrine alkaloids is generally ephedrine (Ref. 82). The comments pointing to evidence of differences in the effects of different ephedrine alkaloids do not provide a basis to conclude that dietary supplements containing ephedrine

alkaloids do not present an unreasonable risk of illness or injury.

(Comment 26) Some comments argued that the scientific literature indicates that single doses of ephedrine up to 60 mg generally do not increase blood pressure (Ref. 83). Other comments cited a handbook of intravenous drug therapy for nurses that states that ephedrine is of low toxicity. One comment stated that the scientific literature describing the effects of ephedrine in doses of 50 to 150 mg does not support the contention that ephedrine in dosages of 50 to 150 mg per day would represent a health hazard. Many comments stated that reviews of the literature and other data by independent experts reflect the scientific consensus that ephedrine alkaloids at 25 mg per dose are safe. One comment cited a clinical study of 98 elderly patients undergoing hip surgery who received 0.6mg/kg ephedrine by intramuscular injection. One out of 48 patients in the placebo group and two out of 50 in the ephedrine group experienced increased heart rate or increased systolic blood pressure greater than 20 percent from baseline. The comment concluded that the dosages used are greater than the dosages found in any dietary supplement containing ephedrine alkaloids and that the results of the study are consistent with the conclusion that, as also asserted by other comments, no significant injury has been clearly associated with dietary supplements containing ephedrine alkaloids when used as directed.

We received numerous other comments dealing with the issue of "safe" doses for ephedrine alkaloids in dietary supplement products. Many expressed the view that low doses of ephedrine alkaloids in dietary supplements do not pose a safety concern and should remain on the market.

(Response) We do not agree that the scientific literature indicates that there is a dose of ephedrine or ephedrine alkaloids that does not present a risk of adverse events. Although dosages vary in dietary supplements containing ephedrine alkaloids, most products are labeled with 20-25 mg ephedrine alkaloids per recommended serving and 100-150 mg ephedrine alkaloids per day. Some of the doses described in the comments as safe (50 to 150 mg ephedrine alkaloids per day) are in the range studied by Boozer et al. (90 mg ephedrine alkaloids per day) (Ref. 49) and, thus, could cause an increase in blood pressure, a significant health concern (*see* previous discussion). We also do not agree that some lower dose of ephedrine has been demonstrated not to increase blood pressure and heart rate. The relationship between a given dose of ephedrine and changes in heart rate and blood pressure has been poorly characterized, although it is clear that ephedrine is capable of increasing both. As discussed in the response to comment 23 of this document, the published studies that have found no effects on blood pressure and/or heart rate have had methodological deficiencies that limited their ability to detect such changes. With respect to the clinical study of 98 elderly patients, the failure to find serious adverse events is understandable, as the study was designed to demonstrate that intramuscular ephedrine was effective to prevent hypotension related to spinal anesthesia. The concern that led to the study was adverse events related to an expected decrease in blood pressure resulting from the anesthesia. As would be expected based on the pharmacology of ephedrine, the study showed that ephedrine is effective in maintaining blood pressure in patients receiving spinal anesthesia.

We do not agree with comments that suggest that low doses of ephedrine alkaloids in dietary supplements do not present an unreasonable risk and should remain on the market. Because this issue was raised in comments responding to the June 1997 proposal, we commissioned a scientific review that was placed in the 2000 docket (Refs. 84 and 85). This review concluded that a "safe dose" of ephedrine alkaloids cannot be identified. The review determined that even "a dose of 1.5 mg every 4 hours (a daily dose of 9 mg) would produce cardiovascular effects that may be dangerous alone, or in association with risk factors * * * " (Ref. 84 at p. 6). We also note that in the 1996 FAC meeting, several committee members stated that, based on the available data, no safe level of ephedrine alkaloids could be identified for use in dietary supplements (Ref. 86). Consequently, they recommended removing dietary supplements containing ephedrine alkaloids from the market (Ref. 87). Although the CANTOX Health Sciences International (CANTOX) review attempted to establish a level of ephedrine alkaloids at which there were no adverse effects, we do not consider the information submitted sufficient to establish a "safe" dose (*see* discussion of CANTOX in the response to comment 32 of this document).

(Comment 27) Many comments raised the issue of the safety of dietary supplements containing ephedrine alkaloids for use in sensitive or special populations. A number of comments indicated that certain individuals may be relatively more sensitive to the stimulant effects of ephedrine alkaloids, and as a result, at greater risk for adverse health consequences. One comment from a physician noted that he does not recommend the use of ephedra products by pregnant women. Another comment indicated a particular

safety concern with the use of dietary supplements containing ephedrine alkaloids in older persons; according to the comment, many elderly persons take medications for which the use of dietary supplements containing ephedrine alkaloids would be contraindicated. Citing a survey that indicated that shift workers frequently use stimulants, including ephedrine alkaloids, in combination with coffee, depressants and/or pain relievers that contain caffeine, one comment expressed the view that ephedrine alkaloids pose a significant health risk to the shift worker population (Ref. 88). The comment further submitted that 69 percent of shift workers are overweight, that shift work is likely to involve physical labor, often performed in hot conditions, and that these factors increase the risks of adverse cardiovascular effects when shift workers use ephedrine alkaloids. Other comments stated that the presence or absence of a susceptible population cannot be determined with the available data. Several comments stated that dietary supplements containing ephedrine alkaloids are not for everyone, and consumers should consult a physician prior to use if they have specified preexisting health conditions.

(Response) We agree with the comments that expressed concern about the effects of ephedrine alkaloids on susceptible populations and have previously discussed long-term and short-term risks to susceptible populations in the response to comment 22 of this document. There is every reason to expect that certain populations will be more susceptible to the adverse effects of ephedrine alkaloids and that many such people will not be aware of their greater susceptibility. As noted previously, people with coronary artery disease, early congestive heart failure, and high blood pressure, all of which are more

* * *

performance was assessed in seven studies that were reviewed in the RAND report. The RAND report noted that the effects of ephedrine on exercise performance were most often studied acutely (*e.g.*, 1 to 2 hours after a single dose) (Refs. 21 and 22). The RAND report could identify no studies that assessed the effect of dietary supplements containing ephedrine alkaloids on athletic performance. While the RAND report found that existing data supported a modest effect of synthetic ephedrine alkaloid containing products plus caffeine on athletic performance enhancement in healthy males in the very short term, no data support a sustained improvement in athletic performance over any significant time period. In these studies, the performance enhancement effect was demonstrated only with a combination of synthetic ephedrine and caffeine, not with ephedrine alone. Therefore, since the available evidence does not indicate that ephedrine itself enhances athletic performance, there is no need to address the issue as to whether ephedrine is a good surrogate for ephedra in evaluating athletic performance enhancement with the use of dietary supplements containing ephedrine alkaloids.

We determined that certain labeling claims made by manufacturers of dietary supplements containing ephedrine alkaloids for athletic performance enhancement were unsubstantiated in light of the findings in the RAND report. These claims were the subject of warning letters sent to various manufacturers in February and March 2003 (available at http://www.fda.gov/bbs/topics/NEWS/ephedra/letterslist.html (list of firms) and http://www.fda.gov/bbs/topics/NEWS/ephedra/warning.html (sample letter).

3. Eased Breathing

We are aware that there are teas and other types of dietary supplements containing ephedrine alkaloids marketed with claims such as "eased breathing" or "better breathing." There are no data that support a benefit to breathing from dietary supplements containing ephedrine alkaloids in healthy people. Moreover, because healthy people are able to breathe without difficulty, we do not believe there is any respiratory benefit in the absence of a disease state (*e.g.*, asthma or a respiratory infection). We note that claims to treat or mitigate a disease, or the effects of a disease, subject a product to regulation as a drug under the act.

4. Other Uses

We are also aware that dietary supplements containing ephedrine alkaloids are promoted for other uses, such as to "feel better," "feel more alert," and "energized." Effects such as "feel better" are subjective in nature and difficult to quantify. The agency is unaware of any data substantiating these types of subjective effects. Effects such as "alertness" and "energy" are consistent with the pharmacological properties of ephedrine alkaloids, although we are not aware of any studies evaluating ephedrine alkaloid products for these uses. Effects like alertness and energy may be of modest benefit to the individual (if they occur), but such effects are temporary and do not improve health. Any such temporary benefits must be weighed against the health risks discussed in section V.B of this document, which can result in long-term or permanent, serious adverse health effects.

D. Do Dietary Supplements Containing Ephedrine Alkaloids Present an Unreasonable Risk?

1. What Does "Unreasonable Risk" Mean?

A threshold issue is the legal standard of "significant or unreasonable risk of illness or injury" (section 402(f)(1)(A) of the act). By its plain language, this standard requires evidence of "significant or unreasonable risk of illness or injury" (emphasis added)." There is no requirement that there be evidence conclusively demonstrating causation of actual harm in specific individuals. In our evaluation of "significant or unreasonable risk," we can consider any relevant evidence, including scientific data about the toxicological properties of a dietary ingredient or its mechanisms of action; scientific information about the well-known effects of pharmacologically-related compounds, including those regulated as drugs; the results of clinical studies, including observational studies; and adverse event reports that have been subject to sound scientific analysis. The Government's burden of proof for "significant or unreasonable risk" can be met with any science-based evidence of risk, without the need to prove that the substance has actually caused harm in particular cases.

Thus, a dietary supplement that caused a sustained rise in blood pressure across the population would increase the risk of cardiovascular events including stroke, heart attack, or death to that population. Even risks that may not be detectable in small studies or studies of short duration could, over time, and on a population-wide basis, result in hundreds or thousands of adverse events. The Government's burden of proof for "unreasonable risk" is met when a product's risks outweigh its benefits in light of the claims and directions for use in the product's labeling

or, if the labeling is silent, under ordinary conditions of use.

(Comment 59) Most comments that articulated a view agreed with the general notion that we must consider a risk-benefit calculus to determine whether dietary supplements containing ephedrine alkaloids present an unreasonable risk, although the comments differed as to how to perform such a calculus and as to the conclusion about whether the risks of these products outweigh their benefits. Several comments agreed with our interpretation, as published in (Ref. 132), that a "significant or unreasonable risk" exists when a product's risks outweigh its benefits, based on the available scientific evidence, in light of the claims the product makes and in light of the products being directly sold to consumers without medical supervision. One comment from a public interest group stated that this interpretation represents a reasonable and practical interpretation of the act that offers some protection to consumers. One comment argued that this interpretation is not permissible under *Chevron U.S.A., Inc.* because we have never adopted a risk-benefit calculus in assessing the safety of foods and because the legislative history of DSHEA does not indicate any Congressional intent to establish a risk-benefit analysis for dietary supplements. The comment stated that we should determine whether risks are "unreasonable" without resorting to an assessment of the benefits of the product.

(Response) We agree with the comments stating that a risk-benefit calculus is appropriate to determine whether dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling, or if no conditions of use are suggested or recommended in the

labeling, under ordinary conditions of use. The relevant analysis for evaluating an agency's interpretation of a statute is set forth in *Chevron U.S.A., Inc.* v. *Natural Resources Defense Council*, 467 U.S. 837 (1984). Under *Chevron*, the first question is whether Congress has directly spoken to the precise question at issue (Step 1). If so, the agency must implement the unambiguous intent of Congress *Id.* at 842-843. If Congress has not directly spoken to the precise question at issue, our interpretation will be upheld as long as it is based on a "permissible construction" of the statute (Step 2) *Id.* at 843-844.

In determining whether Congress has specifically addressed the question at issue, "courts must exhaust the traditional tools of statutory construction, including looking at the statute's text, structure, and legislative history." *Chevron* v. *Federal Energy Regulatory Commission*, 193 F.Supp.2d 54, 67 (D.D.C. Cir. 2002). Section 402(f)(1)(A) of the act states that a dietary supplement is adulterated if it presents a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or, if the labeling is silent, under ordinary conditions of use. The plain meaning of the statute is the starting point of statutory interpretation. (*See* 2A SUTHERLAND STATUTORY CONSTRUCTION 81 (5th ed. 1992).) The words "significant" and "unreasonable" have two different meanings. "Significant" involves an evaluation of risk alone. The plain meaning of "unreasonable," on the other hand, connotes comparison of the risks and benefits of the product. A risk could be significant but reasonable if the benefits were great enough to outweigh the risks. That "unreasonable risk" entails a balancing test in which the benefits of the product or activity are weighed against its dangers is well-established in tort law (*See*

PROSSER AND KEETON ON THE LAW OF TORTS, Sec. 31, at 173 (5th ed. 1984).)

In assessing whether Congress has clearly spoken to the question at issue, a court "should not confine itself to examining a particular statutory provision in isolation. Rather, it must place the provision in context, interpreting the statute to create a symmetrical and coherent regulatory scheme" (*FDA* v. *Brown and Williamson Tobacco Corp.*, 529 U.S. 120, 121 (2000)). The term "unreasonable risk" is used in other provisions of the act, *e.g.*, in the provisions related to medical devices. In the medical device classification provisions, Class III devices are distinguished from Class I and Class II devices in part because they present a "potential unreasonable risk of injury or illness." The legislative history of the device provisions provides some indication of how Congress intended FDA to interpret the term "unreasonable risk in this context. The House Committee Report states: "the requirement that a risk be unreasonable contemplates a balancing of the possibility that illness or injury will occur against the benefits of use" (H. Rept. 853, 94th Cong., 2d Sess. 19 (1976)). Therefore, "unreasonable risk" in the context of classification of medical devices is properly interpreted to require a risk-benefit calculus. There is nothing in the provisions of the act dealing with dietary with dietary [sic] supplements, or the legislative history thereof, that would suggest that FDA should interpret the term "unreasonable risk" in the context of dietary supplements differently than it does in the context of medical devices.

An interpretation of unreasonable risk as entailing a balancing of the risks and benefits of the product is also consistent with the interpretation of other similar statutory provisions outside the act. The Toxic Substances

Control Act contains an "unreasonable risk" standard, and legislative history indicates that Congress intended that this standard be evaluated through a balancing test (*e.g.*, H. Rept. 94-1341, 94th Cong., 2d Sess. 32 (1976)). Indeed, it is difficult to construct an alternative formulation for the phrase "unreasonable risk."

Based upon the plain meaning of "unreasonable risk," the judicial interpretation of that phrase, and legislative history interpreting "unreasonable risk" in other contexts, including the device provisions of the act and other statutes, we conclude that Congress unambiguously intended that an assessment of "unreasonable risk" in the dietary supplement context should entail a risk-benefit analysis.

In the alternative, if a court were to find that Congress has not directly spoken to the issue of whether "unreasonable risk" in the dietary supplement context is demonstrated by balancing risks and benefits, our interpretation of an ambiguous provision should receive deference so long as it is "permissible" (Chevron Step 2). In interpreting ambiguous statutory language, we are guided by the same criteria we evaluated in Step 1 of the Chevron analysis, i.e., the statute's text, structure, history, and purpose (*See Bell Atlantic Telephone Cos.* v. *FCC*, 131 F.3d 1044, 1049 (D.C. Cir. 1997); *Chevron U.S.A., Inc.* v. *FERC*, 193 F. Supp. 2d at 68). Our interpretation of the "unreasonable risk" standard for dietary supplements as requiring a comparison of the risks and benefits of use is consistent with the purpose of the act, as amended by DSHEA, to promote public health and safety. This interpretation is also consistent with the legislative history of the medical device classification provisions. Therefore, our interpretation that "unreasonable risk" implies a weighing

of the risks and benefits of use is, at a minimum, a "permissible construction."

In the absence of explicit standards for the evaluation of "unreasonable risk," one comment urged us to be guided by precedent from other agencies. The comment highlighted the Consumer Product Safety Act (CPSA), its implementing regulations, and related case law. The comment stated that any assessment of "unreasonable risk" must include a balancing of risks and benefits, a stringent burden on us to demonstrate that the product poses an unreasonable risk of injury, evidence other than consumer complaints, and valid scientific data sufficient to predict how likely an injury is to occur. (Citing *Gulf South Insulation* v. *CPSC*, 701 F.2d 1137, 1143 (5th Cir. 1983)), (citing *Aqua Slide 'N' Dive* v. *CPSC*, 569 F.2d 831, 838 (5th Cir. 1978)), the comment stated, "[T]he ultimate question in assessing unreasonable risk is whether the record contains 'such relevant evidence as a reasonable mind might accept as adequate to support a conclusion.'" The comment acknowledged differences in the statutes, including the explicit statutory requirement in CPSA that the regulation impose the least burdensome requirement that prevents or adequately reduces the risk injury for which the rule is being issued (15 U.S.C. 2058(f)(3)(F)). The comment also cited Consumer Product Safety Commission (CPSC) case law stating that reliable evidence of the likely number of injuries is necessary to determine whether a risk is unreasonable (*Southland Mowor Co.* v. *CPSC*, 619 F.2d 499, 510 (5th Cir. 1980)).

(Response) We do not agree that our interpretation of "unreasonable risk" must be confined to the view reflected in the CPSC case law cited by the comment. We have concluded, based on a *Chevron* analysis, that Congress

expressly intended "unreasonable risk" to entail a risk-benefit analysis (*see* the response to comment 59 of this document). In the alternative, if the term "unreasonable risk" is ambiguous, we may interpret its meaning under *Chevron*. As the comment noted, CPSA contains an extensive list of findings that the CPSC must make, based on substantial evidence, before concluding that a consumer product poses an unreasonable risk, including, for example: (1) The degree and nature of the risk of injury the rule is designed to eliminate or reduce; (2) the approximate number of consumer products, or types or classes thereof, subject to such rule; and (3) any means of achieving the objective of the order while minimizing adverse effects on competition or disruption or dislocation of manufacturing and other commercial practices (15 U.S.C. 2058(f)(1) and (f)(3)). The requirements imposed on CPSC in the cases that the comment cited are based on the explicit requirements of CPSA. In contrast, the adulteration provision in section 402(f)(1)(A) of the act does not require that we make any such findings. Like section 402(f)(1)(A) of the act, other parts of the act that require an evaluation of unreasonable risk, such as the device classification and banning provisions, also do not require that we make the findings set forth in CPSA. Had Congress intended that FDA make specific findings such as the degree of risk of injury, it could have so directed in the act; however, it did not. Our conclusion that dietary supplements containing ephedrine alkaloids present an unreasonable risk is based upon our finding that the risks of heart attack, stroke, and death outweigh the minimal benefits conferred by the supplements. Our conclusion is consistent with Congress's express intent in section 402(f)(1)(A) of the act.

(Comment 60) One comment by a health professional group stated that unreasonable risk likely exists when there is no information that substantiates a clear therapeutic benefit or describes a predictable relationship between exposure (dose) and response, and when the appropriate product dose is not known or achievable.

(Response) We agree that unreasonable risk exists when a dietary supplement presents a risk to health, and there is no information substantiating a benefit sufficient to outweigh that risk. In this rulemaking, we base our determination that dietary supplements containing ephedrine alkaloids present an unreasonable risk under section 402(f)(1)(A) of the act on a risk-benefit analysis, finding that the risks of heart attack, stroke, and death outweigh the benefits that may result from such products. In the absence of a use that results in a benefit that outweighs the risks of these products, we conclude that all such products pose an unreasonable risk. We therefore need not determine whether an unreasonable risk exists when the precise relationship between exposure and response is not predictable or when the appropriate product dose is not known or achievable.

(Comment 61) Several comments stated that proof of causation is required to establish unreasonable risk.

(Response) We do not agree that proof of causation is required to establish unreasonable risk under section 402(f)(1)(A) of the act, and conclude that the plain meaning of the standard precludes such an interpretation. In determining whether Congress has specifically addressed the question at issue, "courts must exhaust the traditional tools of statutory construction, including looking at the statute's text, structure, and legislative history" (*Chevron*

U.S.A., Inc. v. *FERC*, 193 F.Supp. 2d at 67). The plain meaning of the statute is the starting point for an analysis of legislative intent. The most applicable definition of the word "risk" in Merriam Webster's Collegiate Dictionary is "possibility of loss or injury" (Merriam Webster's Collegiate Dictionary, 10th ed. 1008 (2002)) (emphasis added). Black's Law Dictionary defines "risk," in part, as follows: "In general, the element of uncertainty in an undertaking; the possibility that actual future returns will deviate from expected returns. Risk may be moral, physical, or economic." Black's Law Dictionary, 6th ed. 1328 (1990) (emphasis added). The words "possibility" and "uncertainty" in these definitions indicates that proof of a definitive causal relationship between the product and illness or injury is not required under section 402(f)(1)(A) of the act. If Congress had intended that definitive proof that a dietary supplement causes harm be a requirement for a showing of adulteration, it would not have used the word "risk" in the statute, and would have instead provided that a dietary supplement is adulterated if it "causes" illness or injury. This interpretation is consistent with other parts of the act, as interpreted in legislative history and case law. For instance, the legislative history of the medical device banning provisions, which require a showing of "substantial deception or an unreasonable and substantial risk of illness or injury" states that "[A]ctual proof of deception or injury to an individual is [not] required" (Section 516 of the act (21 U.S.C. 360f), H. Rept. 853, 94th Cong., 2d Sess. 19 (1976)). Case law on medical device classification also supports that we need not have causal evidence of harm (*See Lake* v. *FDA*, 1989 WL 71554 (E.D. Pa.)) (upholding FDA's finding of unreasonable risk where the risks were unknown and the benefits unproven)). Therefore, we conclude that Congress has spoken clearly and unambiguously that proof

of causation is not required to show that a dietary supplement presents an "unreasonable risk" under section 402(f)(1)(A) of the act.

Our interpretation is also consistent with other statutes that regulate public health risks, most notably TSCA (15 U.S.C. 2601 *et seq.* (1976)). TSCA authorizes the EPA to place restrictions on chemical substances if it finds that " * * * there is a reasonable basis to conclude that the [chemical substance] presents or will present an unreasonable risk of injury to health or the environment" (*Id.* Sec. 2605(a)). The legislative history of this provision states:

This standard for taking action recognizes that factual certainty respecting the existence of an unreasonable risk of a particular harm may not be possible and the bill does not require it. Further, regulatory action may be taken even though there are uncertainties as to the threshold levels of causation. (H. Rept. 94-1341, 94th Cong., 2d Sess. 25 (1976)).

(Comment 62) Several comments stated that any FDA regulatory approach to dietary supplements containing ephedrine alkaloids must consider both risks and benefits, and moreover, that we should determine, based on scientific evidence, a risk-benefit ratio for assessing their safety. These comments suggested that, if we were to set a break-even point, a decision matrix should be established along the following lines: (1) A benefit-to-risk ratio below the break-even point would mean that the risks outweigh the benefits and this would justify either a decision to (a) ban dietary supplement products containing ephedrine alkaloids or (b) restrict access to a case-by-case-basis, i.e., prescription; (2) a benefit-to-risk ratio in excess of the

break-even point would mean that the benefits outweigh the risks and this would justify continued availability, with appropriate warning labels, dosage instructions, etc.; and (3) a benefit-to-risk ratio equal to the break-even point would mean that the risks equaled the benefits and this would justify either (a) continued availability under the present regulatory framework with appropriate labeling or (b) prescription-only access, whereby a medical professional would make the decision as to whether or not the product was appropriate for an individual consumer on a case-by-case basis.

One comment by a medical association stated that, because dietary supplements are classified as foods, and therefore are assumed to be safe, it is imperative that such products have no risks and provide some benefit to consumers. More specifically, the comment stated that dietary supplements containing ephedrine alkaloids should be safer than drugs and should have a much higher overall benefit/risk ratio when compared to drugs.

(Response) We agree that in regulating dietary supplements, we should consider both risks and benefits. As discussed previously in this document, we also agree that we should weigh risks and benefits when evaluating the safety of dietary supplements under the adulteration standard in section 402(f)(1)(A) of the act. With regard to the comment from the medical association, we agree in part and disagree in part. Although the comment is correct that dietary supplements are classified as foods, we do not agree that they are required to have no risks at all. Section 402(f)(1)(A) of the act provides that a dietary supplement is adulterated if it "presents a significant or unreasonable risk of illness or injury" (emphasis added) as labeled, not if it presents any risk at all. Accordingly, risks

that are insignificant and reasonable in light of the benefits from the supplement would not render a dietary supplement adulterated. Further, we note that conventional foods are not always risk-free. With regard to the comment's statements that dietary supplements should be safer than drugs and have a higher overall benefit/risk ratio than drugs, we do not believe it is necessary to reach these issues. For purposes of this rulemaking, we are considering whether the known and reasonably likely risks of dietary supplements containing ephedrine alkaloids outweigh their known and reasonably likely benefits. It is not necessary to determine generally how the risk/benefit ratio of dietary supplements should compare to that of drugs.

2. Do Dietary Supplements Containing Ephedrine Alkaloids Present an Unreasonable Risk Under Labeled or Ordinary Conditions of Use?

(Comment 63) Several comments stated there is enough evidence, both scientific and anecdotal, to conclude that the risks of taking dietary supplements containing ephedrine alkaloids are so severe and reported adverse events sufficiently numerous to conclude that the risks clearly exceed the benefits because either there are no benefits or the benefits are unsubstantiated or modest for both efficacy and duration. These comments included references to support their conclusions. Some cited the RAND report's conclusions regarding the very modest benefit for short-term weight loss and the questionable benefit for other uses; according to the comments, these limited or questionable benefits are far outweighed by adverse events observed in clinical trials. Other references

submitted by these comments included (Refs. 19, 34, 42, and 133 through 136).

Several comments argued that the harm caused by certain medical conditions – for example, obesity – is so severe as to render the unsubstantiated (in the commenter's view) risks of taking dietary supplements containing ephedrine alkaloids insignificant relative to the benefits that would accrue from use of these products. In this view, the weight loss benefit would exceed any potential risk from taking the product and the risk is not unreasonable when compared to the harm caused by obesity. Several comments cited the prevalence of obesity and an increase in obesity over time, and urged us not to take away one important tool for consumers to address the problem. Two comments cited statistics showing that 54 percent of adults are obese in the United States, that the prevalence of obesity increased by 30 percent from 1980 to 1994, and that in 1997 the Centers for Disease Control and Prevention (CDC) attributed 42 percent of deaths to conditions that typically result from obesity. One comment stated that the risks due to obesity are a greater danger than the rare incidences of stroke or heart attacks attributed to dietary supplements containing ephedrine alkaloids.

Other comments concluded that dietary supplements containing ephedrine alkaloids do not present an unreasonable risk because the risks do not outweigh the benefits. They argued that while the benefits of dietary supplements containing ephedrine alkaloids are substantiated, the adverse events reported are either mild, anecdotal, or unsubstantiated and not scientifically valid. Some comments cited the RAND report to support the benefit of ephedrine alkaloids for short-term weight loss

and the lack of adverse effects in clinical trials. The comments assert that only a speculative risk for serious adverse events exists and that RAND concluded that an assessment of case reports is insufficient to reach conclusions regarding causality.

(Response) We have carefully reviewed the preceding comments, and note that many of these issues have been addressed in more detail in the scientific evaluation sections V.B and C of this document. Based on the scientific data and information discussed in those sections, we have concluded that dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury under conditions of use recommended or suggested in their labeling, or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use. As discussed in the responses to comments 34 and 35 of this document, even if we were to extrapolate from data demonstrating effectiveness of certain ephedrine drug products when considering the reasonably likely benefits of dietary supplements containing ephedrine alkaloids, we conclude that the known and reasonably likely risks would outweigh even such extrapolated benefits. A summary of our rationale for reaching this conclusion is presented in our analysis below.

a. *Summary of risks for dietary supplements with ephedrine alkaloids.* People who use dietary supplements containing ephedrine alkaloids are at increased risk for serious adverse events, including heart attack, stroke, and death. Susceptible individuals (*e.g.*, those with coronary artery disease or heart failure), many of whom may not know they have underlying illnesses, are at increased risk for adverse events because these products can cause abnormal heart rhythms (pro-arrhythmic effect), even

when the product is ingested at recommended doses over a short course (one or a few doses). Over longer periods of use, the risk for adverse health effects to the general population, including susceptible individuals, increases further due to a sustained elevation in blood pressure. This is a characteristic effect of the sympathomimetic class of pharmacological compounds. Moreover, the results of *Boozer, et al.* (2002) demonstrate that weight loss achieved with botanical ephedrine alkaloids does not produce the expected decrease in blood pressure (Ref. 49). The risk of experiencing harmful effects from elevated blood pressure increases the longer the blood pressure remains high, and such adverse effects are likely to occur sooner in individuals with hypertension, many of whom are unaware of their illness.

b. *Summary of known and reasonably likely benefits for dietary supplements containing ephedrine alkaloids.* As discussed in the following paragraphs, we conclude, based on all available information and data reviewed in this rulemaking, that these products do not provide a meaningful health benefit. The best clinical evidence for a benefit is for weight loss, but even there the evidence supports only a modest short-term weight loss insufficient to positively affect cardiovascular risk factors or health conditions associated with being overweight or obese. Other possible benefits, such as enhanced athletic performance, enhanced energy, or a feeling of alertness, lack scientific support and/or they would provide only temporary benefits that are trivial in comparison to the risks of serious long-term or permanent consequences like heart attack, stroke, and death.

i. *Weight loss.* As discussed previously, the RAND report provides the most comprehensive review of efficacy

studies for ephedrine alkaloid containing products. The RAND report found evidence that supported an association between short-term use of ephedrine, ephedrine plus caffeine, or dietary supplements that contain ephedrine alkaloids with or without herbs containing caffeine, and a statistically significant increase in short-term weight loss compared to placebo. The RAND report concluded that products containing ephedrine alkaloids in combination with caffeine resulted in a modest weight loss of approximately 2 pounds per month more than placebo over a period of 4 to 6 months. RAND concluded that the use of ephedrine without caffeine was associated with a statistically significant increase in weight loss (1.3 pounds of weight loss per month) compared with that of placebo for up to 4 months of use. RAND identified a single trial of 3 months duration that assessed the effect of herbal ephedra versus placebo. Those in the ephedra arm lost 1.8 pounds more per month than did those in the placebo arm. We are unaware of any appropriate, well-designed studies showing an effect of dietary supplements containing ephedrine alkaloids on weight loss for more than 6 months. Such a long-term effect would be necessary to translate into health outcome improvements.

Even if there were adequate substantiation that dietary supplements containing ephedrine alkaloids produce long-term, sustained weight loss in the overweight or obese population, the long-term risks posed by these products, particularly in obese patients who may already have underlying illnesses that can be aggravated by these products (such as hypertension), remain a serious concern. We believe that physician supervision is necessary to mitigate the risks associated with the use of sympathomimetic products in the long term for weight loss

and the treatment of obesity, or for any other long-term use. This is achieved in part by monitoring patients who use these products and discontinuing product use if the patient develops hypertension, experiences other adverse health effects, or fails to achieve weight loss that would justify continued exposure to the risks associated with use of the product.

People might choose to use a dietary supplement containing ephedrine alkaloids to lose weight for purposes other than to improve health (*e.g.*, to look slimmer or fit into an outfit for a special occasion), and we do not dismiss this use as without value to the individual. To achieve the result of modest weight loss, however, these products must be used over a period of months. Individuals who use these dietary supplements over a period of months for weight loss are at risk for the adverse events that can occur with both short- and long-term use of these products. These risks are greater than the modest benefits described in the RAND report.

In the case of both short-term and long-term use, any benefits of dietary supplements containing ephedrine alkaloids for weight loss are outweighed by their risks. Therefore, we conclude that dietary supplements containing ephedrine alkaloids labeled or used for weight loss present an unreasonable risk.

ii. *Enhancement of athletic performance.* The effects of synthetic ephedrine on athletic performance were assessed in seven studies that were reviewed in the RAND report. Despite the widespread marketing of products containing ephedrine alkaloids as performance-enhancers, the RAND report found no studies involving botanical ephedrine alkaloids, and very limited evidence

involving synthetic ephedrine, to support the claims. Furthermore, the RAND report concluded that, "to show even a short-term effect of ephedrine, combination with caffeine was required." Therefore, there is no evidence to indicate that ephedrine alone enhances athletic performance. People who use dietary supplements containing ephedrine alkaloids for athletic performance are at risk for the same serious adverse events as individuals who use these products for other indications. As discussed previously in section V.C.2, the available evidence regarding a possible benefit from these products for enhancing athletic performance is further limited: the supporting evidence all comes from studies in which synthetic ephedrine and caffeine in combination were administered to healthy males, and the modest effects shown were in the very short term only. Even if one could disregard all the gaps in the scientific evidence and assume that ephedra has the same effect on athletic performance as synthetic ephedrine in combination with caffeine, we do not consider a modest, temporary enhancement of certain aspects of athletic performance to be a benefit sufficient to outweigh the risks of dietary supplements containing ephedrine alkaloids. Therefore, we conclude that the use of dietary supplements containing ephedrine alkaloids to enhance athletic performance for any duration of use present an unreasonable risk.

iii. *Eased breathing and other uses.* We have long recognized the legitimate short-term oral use of sympathomimetics, such as ephedrine, in OTC bronchodilator drug products. These products are marketed for those who have been diagnosed with asthma by a physician. The products are GRASE when formulated and labeled in accordance with the requirements of the final monograph for OTC

bronchodilators (21 CFR part 341). Mandatory warnings include advising the consumer not to use the product unless diagnosed as having asthma by a doctor and not to use the product if suffering from heart disease or high blood pressure.

We are aware that there are dietary supplements containing ephedrine alkaloids that are marketed for uses other than weight loss or athletic performance enhancement, such as "eased breathing," "better breathing," "feel better," "feel more alert," "energized." By contrast to the monograph-compliant OTC bronchodilators, and as discussed in section V.B.3 of this document, we have seen no data that support any benefit relating to eased breathing in healthy people from dietary supplements containing ephedrine alkaloids. Moreover, as also discussed in that section, because healthy people are able to breathe without difficulty, we do not believe there is any respiratory benefit in the absence of a disease state, such as asthma or a respiratory infection. At the same time, however, there are data that establish the risks of these products. We note that claims to treat or mitigate the effects of a disease subject a product to regulation as a drug under the act.

With regard to other claims such as "feel better," "feel more alert," and "energized," effects of this nature may be of modest benefit to the individual (if they occur), but they are temporary and do not improve health. Therefore, such effects would not be sufficient to outweigh the risks of dietary supplements containing ephedrine alkaloids.

There are also dietary supplements containing ephedrine alkaloids that do not make any specific claims or otherwise suggest or recommend conditions of use in their labeling. The use of such products presents the same risks

and can lead to the same serious adverse events as discussed previously for weight loss and athletic performance, even if the product is taken under ordinary conditions of use (i.e., not abused).

A dietary supplement labeled for a very temporary, episodic use might not present an unreasonable risk if there were adequate evidence that the use resulted in a health benefit sufficient to outweigh the health risks. Any new indication would still be subject to our post-market risk evaluation as to whether it could be legally marketed. Conclusions regarding the benefit of dietary supplements containing ephedrine alkaloids for nondisease claims cannot be drawn solely from studies using synthetic ephedrine for specific diseases. Although we could require labeling for dietary supplements containing ephedrine alkaloids to limit the duration of use, among other things, currently there are no data that demonstrate that dietary supplements containing ephedrine alkaloids provide a benefit to a particular population when used temporarily or episodically (in contrast to OTC ephedrine and pseudoephedrine products for disease uses).

3. Conclusion

Multiple studies demonstrate that dietary supplements containing ephedrine alkaloids, like other sympathomimetics, raise blood pressure and increase heart rate. These products expose users to several risks, including the consequences of a sustained increase in blood pressure (*e.g.* serious illnesses or injuries that include stroke and heart attack that can result in death) and increased morbidity and mortality from worsened heart failure and pro-arrhythmic effects. Although the pro-arrhythmic

effects of these products typically occur only in susceptible individuals, the long-term risks from elevated blood pressure can occur even in nonsusceptible, healthy individuals. These risks are neither outweighed by any known or reasonably likely benefits when dietary supplements containing ephedrine alkaloids are used under conditions suggested or recommended in their labeling, such as for weight loss, athletic performance, increased energy or alertness, or eased breathing. Nor do the benefits outweigh the risks under ordinary conditions of use, in the absence of suggested or recommended conditions of use in product labeling. As discussed above in section V.C of this document, the best scientific evidence of benefit is for modest short-term weight loss; however, such benefit would be insufficient to bring about an improvement in health that would outweigh the concomitant health risks. The other possible benefits discussed in section V.C of this document, have less scientific support. Even assuming that these possible benefits in fact occur, such temporary benefits are also insufficient to outweigh health risks that can lead to serious long-term or permanent consequences like heart attack, stroke, and death. On the other hand, we have determined that there are benefits from the use of OTC and prescription drug products containing ephedrine alkaloids in certain populations for certain disease indications that outweigh their risks.

As with other sympathomimetics, the risks posed by dietary supplements containing ephedrine alkaloids for continuous, long-term use cannot be adequately mitigated without physician supervision. Temporary, episodic use can be justified only if a known or reasonably likely benefit outweighs the known and reasonably likely risks. Similar to OTC single ingredient ephedrine products, dietary

supplements containing ephedrine alkaloids could theoretically be marketed without physician supervision for a very temporary, episodic use if there were adequate evidence that the use resulted in a benefit sufficient to outweigh the risks of these products. However, we are currently unaware of any such use, and our experience with ephedrine and pseudoephedrine OTC drug products suggests that such benefits will be demonstrable only for disease uses. Therefore, we conclude that dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or under ordinary conditions of use, if the labeling does not suggest or recommend conditions of use.

VI. Why We Conclude that Other Restrictions Would Not Adequately Protect Consumers from the Risks Presented by Dietary Supplements Containing Ephedrine Alkaloids

We considered several regulatory alternatives to this final rule. As discussed in section I.C of this document, we issued a proposed rule in 1997 that would have placed various restrictions on dietary supplements containing ephedrine alkaloids. Most of the proposed restrictions were withdrawn in 2000; only the proposed prohibition on combining ephedrine alkaloids with other stimulant ingredients and the proposed warning statement (as modified in FDA's March 2003 notice) remain. As discussed in the following paragraphs, we have reached the conclusion that those restrictions are inadequate to protect public health. In addition, we considered other regulatory alternatives presented in the comments received.

A. Warning Statement Alone

We first proposed a warning statement in the June 1997 proposal. At that time, we tentatively concluded that a warning statement was necessary to disclose material facts about the consequences of using these products, and that it would help to reduce the risk of an adverse event after use of dietary supplements containing ephedrine alkaloids (62 FR 30670 at 30703). In our March 2003 notice, we reopened the comment period to seek, among other things, comments on a revised warning statement that we were considering at that time for dietary supplements containing ephedrine alkaloids.

We received a number of comments on the proposed labeling requirements in the June 1997 proposal and on the revised warning statement in our March 2003 notice. Because we have decided to proceed under the adulteration provision in section 402(f)(1)(A) of the act rather than to require labeling for dietary supplements containing ephedrine alkaloids, these comments are moot to the extent that they discuss the substance or format of the warning statement. Nevertheless, comments regarding the sufficiency of a warning are relevant to this rulemaking.

(Comment 64) Many comments supported the use of a warning label as an effective way to protect public health, although they differed on the specific language and format of the warning. Many comments urged us to mandate strict warning labels to inform users about the potential health risks that have been reported to be associated with the use of dietary supplements containing ephedrine alkaloids. One comment stated that product labeling does influence user behavior and strongly urged us to take action in the form of issuing a mandatory warning label

for all dietary supplements containing ephedrine alkaloids. Several comments stated that there was a significant decrease in the number of AERs in certain States after their respective departments of health mandated label restrictions and strong cautionary statements. A number of comments stated that the warning labels voluntarily adopted and already used by industry are sufficient to protect the public from any risks. A number of comments proposed different labels to be adopted by the entire industry.

In contrast, many comments maintained that warnings are insufficient and recommended a ban of these products. Several comments pointed out that serious adverse events

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STATUTORY APPENDIX

21 U.S.C. § 321. Definitions; generally

For the purposes of this Act [21 USCS §§ 301 et seq.] –

(g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 403(r)(1)(B) and 403(r)(3) or sections 403(r)(1)(B) and 403(r)(5)(D) [21 USCS § 343(r)(1)(B) and (r)(3) or (r)(1)(B) and (r)(5)(D)], is made in accordance with the requirements of section 403(r) [21 USCS § 343(r)] is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 403(r)(6) [21 USCS § 343(r)(6)] is not a drug under clause (C) solely because the label or the labeling contains such a statement.

(p) The term "new drug" means –

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling

thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act [enacted June 25, 1938] it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

21 U.S.C. § 342. Adulterated food

A food shall be deemed to be adulterated –

(a) Poisonous, insanitary, or deleterious ingredients.

(1) If it bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health.[; or] (2)(A) if it bears or contains any added poisonous or added deleterious substance (other than a substance that is a pesticide chemical residue in or on a raw agricultural commodity or processed food, a food additive, a color additive, or a new animal drug) that is unsafe within the meaning of section 406 [21 USCS § 346]; or (B) if it bears or contains a pesticide

chemical residue that is unsafe within the meaning of section 408(a) [21 USCS § 346a(a)]; or (C) if it is or if it bears or contains (i) any food additive that is unsafe within the meaning of section 409 [21 USCS § 348]; or (ii) a new animal drug (or conversion product thereof) that is unsafe within the meaning of section 512 [21 USCS § 360b]; or (3) if it consists in whole or in part of any filthy, putrid, or decomposed substances, or if it is otherwise unfit for food; or (4) if it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health; or (5) if it is, in whole or in part, the product of a diseased animal or of an animal which has died otherwise than by slaughter; or (6) if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health; or (7) if it has been intentionally subjected to radiation, unless the use of the radiation was in conformity with a regulation or exemption in effect pursuant to section 409 [21 USCS § 348].

(b) Absence, substitution, or addition of constituents. (1) If any valuable constituent has been in whole or in part omitted or abstracted therefrom; or (2) if any substance has been substituted wholly or in part therefor; or (3) if damage or inferiority has been concealed in any manner; or (4) if any substance has been added thereto or mixed or packed therewith so as to increase its bulk or weight, or reduce its quality or strength, or make it appear better or of greater value than it is.

(c) Color additives. If it is, or it bears or contains, a color additive which is unsafe within the meaning of section 721(a) [21 USCS § 379e(a)].

(d) Confectionery containing alcohol or nonnutritive substance. If it is confectionery, and –

(1) has partially or completely imbedded therein any nonnutritive object, except that this subparagraph shall not apply in the case of any nonnutritive object if, in the judgment of the Secretary as provided by regulations, such object is of practical functional value to the confectionery product and would not render the product injurious or hazardous to health;

(2) bears or contains any alcohol other than alcohol not in excess of one-half of 1 per centum by volume derived solely from the use of flavoring extracts, except that this clause shall not apply to confectionery which is introduced or delivered for introduction into, or received or held for sale in, interstate commerce if the sale of such confectionery is permitted under the laws of the State in which such confectionery is intended to be offered for sale; or

(3) bears or contains any nonnutritive substance, except that this subparagraph shall not apply to a safe nonnutritive substance which is in or on confectionery by reason of its use for some practical functional purpose in the manufacture, packaging, or storage of such confectionery if the use of the substance does not promote deception of the consumer or otherwise result in adulteration or misbranding in violation of any provision of this Act [21 USCS §§ 301 et seq.], except that the Secretary may, for the purpose of avoiding or resolving uncertainty as to the application of this subparagraph, issue regulations allowing or prohibiting the use of particular nonnutritive substances.

(e) Oleomargarine containing filthy, putrid, etc., matter. If it is oleomargarine or margarine or butter and any of

the raw material used therein consisted in whole or in part of any filthy, putrid, or decomposed substance, or such oleomargarine or margarine or butter is otherwise unfit for food.

(f) Dietary supplement or ingredient: safety.

(1) If it is a dietary supplement or contains a dietary ingredient that –

(A) presents a significant or unreasonable risk of illness or injury under –

(i) conditions of use recommended or suggested in labeling, or

(ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use;

(B) is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury;

(C) the Secretary declares to pose an imminent hazard to public health or safety, except that the authority to make such declaration shall not be delegated and the Secretary shall promptly after such a declaration initiate a proceeding in accordance with sections 554 and 556 of title 5, United States Code, to affirm or withdraw the declaration; or

(D) is or contains a dietary ingredient that renders it adulterated under paragraph (a)(1) under the conditions of use recommended or suggested in the labeling of such dietary supplement.

In any proceeding under this subparagraph, the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated. The court shall decide any issue under this paragraph on a de novo basis.

(2) Before the Secretary may report to a United States attorney a violation of paragraph (1)(A) for a civil proceeding, the person against whom such proceeding would be initiated shall be given appropriate notice and the opportunity to present views, orally and in writing, at least 10 days before such notice, with regard to such proceeding.

(g) Dietary supplement: manufacturing practices.

(1) If it is a dietary supplement and it has been prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations, including regulations requiring, when necessary, expiration date labeling, issued by the Secretary under subparagraph (2).

(2) The Secretary may by regulation prescribe good manufacturing practices for dietary supplements. Such regulations shall be modeled after current good manufacturing practice regulations for food and may not impose standards for which there is no current and generally available analytical methodology. No standard of current good manufacturing practice may be imposed unless such standard is included in a regulation promulgated after notice and opportunity for comment in accordance with chapter 5 of title 5, United States Code [5 USCS §§ 500 et seq.].

(h) Reoffer of food previously denied admission. If it is an article of food imported or offered for import into the United States and the article of food has previously been refused admission under section 801(a) [21 USCS § 381(a)], unless the person reoffering the article affirmatively establishes, at the expense of the owner or consignee of the article, that the article complies with the applicable requirements of this Act [21 USCS §§ 301 et seq.], as determined by the Secretary.

(i) Unsanitary transport. If it is transported or offered for transport by a shipper, carrier by motor vehicle or rail vehicle, receiver, or any other person engaged in the transportation of food under conditions that are not in compliance with regulations promulgated under section 416 [21 USCS § 350e].

21 U.S.C. § 355. New drugs

(a) Necessity of effective approval of application. No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug.

(b) Filing application; contents.

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; . . .

* * *

(i) Exemptions of drugs for research; discretionary and mandatory conditions; direct reports to Secretary.

* * *

(3)(A) At any time, the Secretary may prohibit the sponsor of an investigation from conducting the investigation (referred to in this paragraph as a "clinical hold") if the Secretary makes a determination described in subparagraph (B). The Secretary shall specify the basis for the clinical hold, including the specific information available to the Secretary which served as the basis for such clinical hold, and confirm such determination in writing.

(B) For purposes of subparagraph (A), a determination described in this subparagraph with respect to a clinical hold is that –

(i) the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved; or . . .

21 U.S.C. § 360c Classification of devices intended for human use

(a) Classes of devices.

* * *

(2) For purposes of this section and sections 514 and 515 [21 USCS §§ 360d, 360e], the safety and effectiveness of a device are to be determined –

(A) with respect to the persons for whose use the device is represented or intended,

(B) with respect to the conditions of use prescribed, recommended, or suggested in the labeling of the device, and

(C) weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.

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